This is to certify that Miss ENA L. BROWN has successfully sustained an oral examination on the subject matter of her thesis by a committee of the Department. The examination was held in January of this year.

Members
of
Committee.

19 March, 1937.

SOME STUDIES In QUALITATIVE ORGANIC CHEMISTRY.

By

ENA LIGHBODY BROWN, B.Sc.

Thesis submitted for the degree of Ph.D.

University of Edinburgh. May 1937.

I N D E X.

INDEX Of PREPARATIONS.

Page.

INDEX Of TABLES.

GENERAL INTRODUCTION.

Qualitative organic analysis has, in recent years, become increasingly important in the training of the organic chemist. The examination of organic compounds has a greater educational value than that of inorganic, owing (due) to the fact that the scheme for analysis is not so definite as that for inorganic. Consequently the student has to depend more on his immediate knowledge of organic chemistry than on following a definite routine. Although very many important advances have been made in the identification of organic compounds there are still many classes of substances which cannot be identified unless by very long, involved methods. In qualitative organic analysis the final test in the identification of any compound is by the preparation of some solid derivative with a definite crystalline structure and melting point. There are already tests for most compounds but many of these could be much improved. For routine work it is quite essential that such derivatives be easily prepared and purified. The 2-4-dinitrophenylhydrazones for aldehydes and ketones and the 3-5-dinitrobenzoates for alcohols are derivatives which have recently been worked out and are great improvements on those previously used.

On the other hand, there are many important compounds which cannot be readily identified, e.g., amyl acetate, ethyl nitrate, oxamide and the alkyl halides.

There are various conditions which a reagent must fulfil before being adopted as the most suitable one for a given class of compounds.

1) It must be easily and cheaply prepared and not undergo changes on keeping: for example, polymerisation, which would make it useless as a reagent, or sensitivity to moisture as in the case of phenylisocyanate.

2) It must be easy to handle - that is, it must not produce any ill effects. For example, phenyl hydrazine must be handled with care and consequently the harmless 2-4-dinitrophenylhydrazine is much to be preferred.

3) The reagent must react rapidly with the substance to be identified so as to give a good yield of derivative.

4) The resulting compounds must be easily isolated and differ in properties from the original compound, and must crystallise rapidly to give good crystals.

5) The melting points of such compounds must be within a certain temperature range of 60°C. to 220°C., so that they are easy to determine. Such melting points must be sharp. Compounds melting below 80°C. are apt to be "oily" and often are difficult to crystallise, while many compounds melting at a higher temperature, e.g., above 220°C., tend to char or to decompose without

having a sharp melting point - e.g., some semicarbazones.

6) The melting points of the derivatives of neighbouring members of a homologous series should differ by at least 5°C. from one another.

The aim of this research has been to find reagents which obey the above rules and are applicable to 0·5 gm. or less of the compound. The reaction must be applicable to a whole class of compounds and not just to one or two members of a series. For example, picric acid forms crystalline picrates with some hydrocarbons like naphthalene, but with benzene and toluene the picrates are so soluble that they are difficult to isolate.

In a recent publication (J.A.C.S., 1935, 57, 940) the statement is found: "There exists at present no satisfactory general method for the identification of substituted aromatic hydrocarbons. Nitration and oxidation to quinones, while being satisfactory procedures in certain cases, do not constitute methods applicable to all compounds of this class. Likewise oxidation of sidechains is not only limited in scope but difficult to carry out on a small scale and valueless in distinguishing hydrocarbons containing different substituents in the sidechain like methyl, ethyl, propyl, etc." Oxidations of sidechains are effected by means of potassium permanganate or chromic acid. The latter is often rather violent, o-xylene giving carbon dioxide

and water. Permanganate does not oxidise every compound. With toluene, for example, it is extremely difficult to effect oxidation, and in the case of m-nitrotoluene there is no appreciable reaction. The procedure is rather lengthy, 4-iodo m-xylene requiring fifty hours. A quotation from a recent book (Mann and Saunders, Pract. Org. Chem., p. 264) stresses this point: "Toluene may be distinguished from benzene in that it gives benzoic acid on oxidation. The reaction, however, takes several hours for completion and hence is of little practical value as a test". Again permanganate oxidations are apt to "bump" when boiling and are not always applicable to small quantities. This latter point is perhaps the most important in present day qualitative analysis when it is advisable that identification methods be applicable on the micro or at least the semi-micro scale. Many valuable compounds are isolated today in minute quantities, e.g., the vitamins, demanding an examination of their properties leading to the proof of their structure.

In the present work oxidation of sidechains has been carried out in sealed tubes with nitric acid of specific gravity 1·2 and is applicable to 0·5 gm. or less. o-Xylene is oxidised by permanganate to phthalic acid but the yield is poor, and by chromic acid to carbon dioxide. On the other hand, sealed tube oxidation at 100°C. yields toluic acid in good quantity

in a short time. Similar results have been obtained with over forty other compounds. The technique and apparatus involved are simple and can easily be used by undergraduate students in the laboratory. It is hoped that eventually the micro scale will be obtained.

There is no standard reagent for the identification of alkyl halides. Those used depend on the formation of the corresponding Grignard Reagent. From this and phenylisocyanate or α-naphthylisocyanate the anilides (Schwartz and Johnston, J.A.C.S., 1931, 53,1063) and α-naphthalides (Hill, J.A.C.S., 50, 167; 47, 3009) can be prepared. The objection to the use of phenylisocyanate is that it is extremely sensitive to moisture and so cannot be easily kept.

$$C_6H_5N{=}C{=}O + H_2O \longrightarrow C_6H_5{\cdot}NH{\cdot}COOH$$

$$C_6H_5NH{\cdot}COOH + C_6H_5{\cdot}NCO \longrightarrow C_6H_5NH{\cdot}CO{\cdot}NHC_6H_5 + CO_2$$

Carbanilide

The process which this involves is long and everything depends on the absence of moisture.

$$R{\cdot}MgX + C_6H_5NCO \longrightarrow C_6H_5N{=}\overset{\overset{R}{|}}{C}{-}OMgX$$

$$C_6H_5{\cdot}N{=}\overset{\overset{R}{|}}{C}{-}OMgX + H_2O \longrightarrow C_6H_5NH\overset{\overset{R}{|}}{C}{=}O + MgXOH$$

Anilide

R = Alkyl group.
X = Halide group.

Similarly for the α-naphthalides.

Young has recently prepared nitrogen substituted sulphonanilides (J.A.C.S., 1934, 56, 2167, 2783; 57, 773)

which give crystalline derivatives with alkyl halides, but these are not altogether satisfactory. An attempt has been made with success in this research to identify alkyl halides by their reaction with Thiourea $NH_2CS\,NH_2$ and the corresponding formation of picrates

$$NH_2 \cdot CS \cdot NH_2 \longrightarrow NH_2 \cdot C(SH)=NH$$

$$NH_2 \cdot C(SH)=NH + RX \longrightarrow NH_2 \cdot C(SR)=NH, HX$$

R = Alkyl group.
X = Halide group.

The reaction depends primarily on the tautomerism of the thiourea to isothiourea with which the halide reacts to form a sulphur substituted isothiourea hydrobromide or iodide. These latter compounds cannot be themselves isolated since they are deliquescent, but in alcoholic solution they react readily with picric acid to form stable picrates with definite melting points and characteristic crystalline structures. The reaction can be completed in about ten minutes in comparison with the several hours of the Grignard process due to the drying, etc., of the apparatus. In the case of alkyl iodides, in the Grignard process a side reaction often takes place.

$$2RI + Mg \longrightarrow R - R + MgI_2$$

Hence the bromides are generally used. Derivatives of alkyl halides are particularly useful, not only because these compounds are frequently encountered but also because they are readily made from alcohols, and so

furnish an indirect way of identifying the alcohols. All the methods used up to the present have had to be used with caution in view of the fact that rearrangements sometimes occur.

Aliphatic primary and secondary amines are not always easy to identify. The standard reagents are picric acid, benzene sulphonyl chloride and phenylisothiocyanate. The picrates are often serviceable but we have found that dilute aqueous or alcoholic solutions do not always yield the picrates. It is better to use benzene sulphonyl chloride to classify primary amines from secondary, than for its derivatives, the sulphonamides, which have rather low melting points.

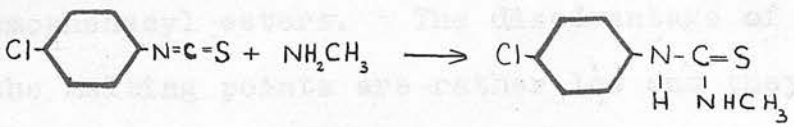
$$C_6H_5SO_2Cl + R{\cdot}NH_2 \longrightarrow C_6H_5SO_2NH{\cdot}R$$

This product is soluble in dilute caustic soda due to the hydrogen atom attached to the nitrogen. The product from secondary amines is insoluble. This is known as Hinsberg's test.

$$C_6H_5SO_2Cl + \begin{matrix} R \\ R \end{matrix}\!\!>\!NH \longrightarrow C_6H_5SO_2N\!<\!\begin{matrix} R \\ R \end{matrix}$$

A less known but nevertheless valuable reagent is phenylisothiocyanate C_6H_5NCS which gives good crystalline derivatives. The melting points in some cases, e.g. propylamine, are rather low and in others, like diethylamine and ethylene diamine, only oils are formed. Substituents in the benzene ring, such as chloro, nitro, methyl, should raise the melting points of the corresponding derivatives which should crystallise

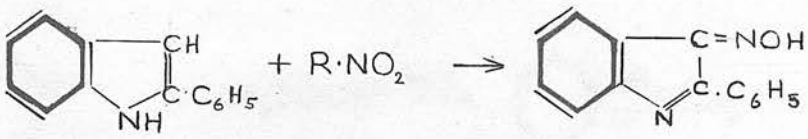
readily. Sah and Lei (Chem. Zent. Blatt, 1934, 2, 3015) used m-nitrophenylisothiocyanate as a reagent for aromatic amines but did not apply it to aliphatic primary and secondary amines. Their derivatives have reasonable melting points, have a definite crystalline structure and can be prepared in a very short time. Morgan (J.C.S., 1931, 1124) used the diphenyl compound, p-xenylcarbimide, with success for polyhydric phenols and also mentions the α-naphthyl compounds. Any of these substituents in phenylisothiocyanate should raise the melting points and so be of greater value in amine identification. The type of compound that is formed is an addition compound and has a definite crystalline structure:



No attempt has been made to form the substituted isothiocyanate derivatives of the aromatic amines as there are already sufficient excellent methods of identification. The acetyl derivatives, the picrates, and the benzenesulphonamides are some of those best known.

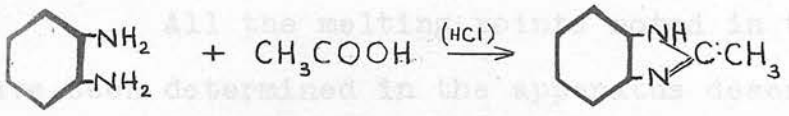
A suitable reagent for the identification of aliphatic nitrites has been found. Nitrites, such as ethyl nitrite, react with α-phenylindole to form a crystalline compound known as β-isonitroso-α-phenylindole, with a definite melting point. It is of use for the

detection of aliphatic nitrites as a class but useless for characterising one member from another. This, however, can generally be determined from the boiling point of the original compound. This reagent should be very useful, as up to the present there is no suitable reagent for classifying nitrites.



The saturated monobasic aliphatic acids which are most frequently encountered are liquids which are volatile with steam and so are often obtained in dilute aqueous solution. There are many methods for their identification, such as the p-nitrobenzyl esters and the p-bromophenacyl esters. The disadvantage of these is that the melting points are rather low and they are not applicable to all members. The method using p-bromophenacyl bromide has the advantage that the acid does not require to be anhydrous. This is very useful because it very often happens that a small sample of acid in aqueous solution requires identification and isolation from the water would give an almost negligible quantity. Phillips (J.C.S., 1928, 2393) has used o-phenylene diamine. Solid derivatives are formed with monobasic acids on boiling with o-phenylene diamine and 4 N. hydrochloric acid. The disadvantage of this is that the melting pointsof the 2-substituted

benziminazoles formed are all about the same. We have tried this on a small scale 0·2 - 0·5 g. and formed the picrate of the benziminazole. The method seems to be quite successful and the melting points of the picrates formed are reasonably far apart.

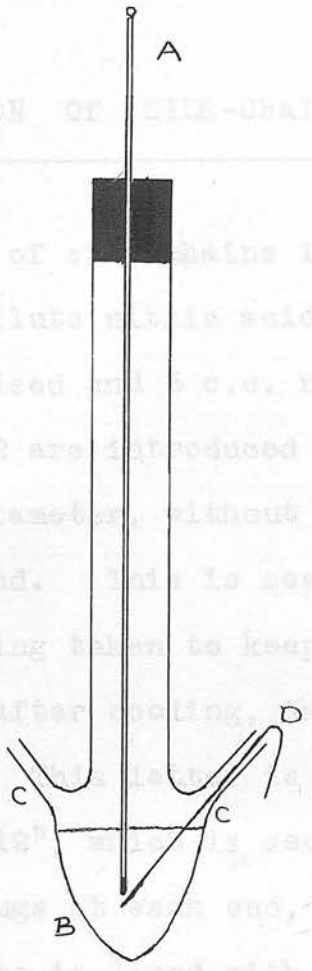


For convenience the practical work of this thesis will be divided into several sections, each having a short introduction and discussion of results.

E X P E R I M E N T A L.

Determination of Melting Points.

All the melting points noted in the thesis have been determined in the apparatus described below. A tube of approximately one inch in diameter with a bulb at the foot and two small side openings, C, is clamped vertically. Concentrated sulphuric acid is put into the bulb which is heated by a small bunsen flame. A thermometer, 360° Centigrade, is suspended in the tube, the foot being immersed in the acid. The substance, the melting point of which is to be determined, is finely ground, thoroughly dried, and introduced into a melting point tube which is then bent, as in diagram, and introduced into the apparatus by one of the side openings C.



A is thermometer.

B is sulphuric acid.

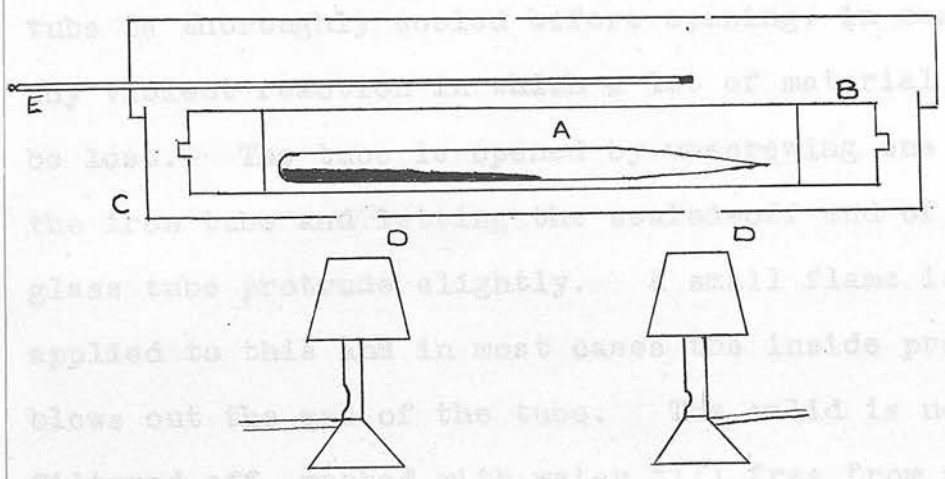
C are side openings for introducing tube.

D is the small melting point tube containing the substance.

The thermometer used throughout was calibrated against small standard thermometers so that all melting points are corrected.

I. OXIDATION Of SIDE-CHAINS.

Oxidation of side-chains is carried out in sealed tubes with dilute nitric acid. 0·5 g. of the compound to be oxidised and 5 c.c. nitric acid of specific gravity 1·2 are introduced into a thick soft glass tube, $\frac{1}{2}$" in diameter, without moistening the walls at the open end. This is sealed off in a blow-pipe flame, care being taken to keep the thickness of the walls equal. After cooling, the tube is placed in an iron "bomb". This latter is a piece of heavy iron tubing, 1" by 12", which is securely closed with solid iron screw plugs at each end, one of which is removable. The tube is lined with asbestos paper. The "bomb" is placed on a small metal support inside an asbestos furnace which is prepared from sheet asbestos, 1/8" thick, and bent into the required shape, 12" × 3" × $2\frac{1}{2}$", by moistening with water the parts which are to be folded over. The box is fixed together by pieces of wire at the joins. The furnace is heated by means of bunsens placed below two small holes in the foot of the box. A lid is prepared in a similar way to fit and has holes at intervals along the top to ensure even heating. A thermometer suspended between the lid and the metal tube registers the temperature.



A is tube containing substance with nitric acid.

B is the iron tube.

C is the furnace.

D are the sources of heat.

E is the thermometer.

After experimenting with time and temperature the best conditions for oxidation were found to be

heating 0·5 g. of the substance with 5 c.c. nitric acid in the sealed tube for 1 hour at 130-150°C. In most cases this has been found satisfactory and in several resistant cases two hours at the same temperature has been successful. After the reaction is completed the tube is thoroughly cooled before opening, in case of any violent reaction in which a lot of material would be lost. The tube is opened by unscrewing one end of the iron tube and letting the sealed-off end of the glass tube protrude slightly. A small flame is then applied to this and in most cases the inside pressure blows out the end of the tube. The solid is now filtered off, washed with water till free from nitric acid and crystallised from water or alcohol. The melting point and yield of the pure compound are then determined and the product confirmed by means of a mixed melting point with a standard specimen of the compound, by formation of an ester, or by a semimicro titration with standard sodium hydroxide when the molecular weight can be determined.

Cohen and Miller (J.C.S., 1904, 85, 74, 1622) have oxidised the bromo, chloro and dihalogen toluenes, and Cohen and Hodsman (J.C.S., 1907, 91, 970) the nitro and chloronitrotoluenes in sealed tubes. They maintain the temperature at 140-150° by suspension of the tube in a vessel containing boiling coal tar naphtha. Their experiments were used for comparison of the rates

of oxidation of the various compounds and not as a means of identification. We have found that the halogen, nitro, mono and disubstituted toluenes are readily oxidised, but that the method is not so satisfactory for the higher substituted compounds. The yields by this method are, in general, extremely good and the product, if well washed with water, relatively pure. The method is also more rapid than that with permanganate or dichromate. For the monosubstituted benzenes, like ethyl benzene and propylbenzene, the method does not serve as a means of identification, since benzoic acid is obtained in each case. By taking the original boiling points and properties into consideration along with the rate of oxidation, a fairly good distinction can be made. It is useful for the xylenes which yield the corresponding toluic acids.

No nitration takes place with the acid of specific gravity 1·2, and in every case the product was tested for nitro groups by means of the colour tests described by Bost and Nicholson (J. Ind. Eng. Chem. (Anal.), 1935, 7, 190). Concentrated nitric acid would tend to favour nitration to a greater extent. Interesting results have been obtained with 4-chloro-m-xylene in the pure state and with a sample containing a trace of dissolved iodine. The first results indicated that it might be a suitable method for the preparation of 4-chloro-3-methylbenzoic acid, but experiments on a

larger scale led to rather contradictory results (see experimental results).

All yields quoted in the experimental results are after purification, and the melting points quoted from the literature are taken from Beilstein's Handbook of Organic Chemistry. In the experimental results, the melting points and yields refer to the product obtained.

Results.

Except when otherwise stated, 0·5 g. of the compound and 5 c.c. nitric acid are heated at 130-150°C for 1 hour.

Toluene. At 100-130°C. a mixture of benzoic acid and benzaldehyde results, but at 130-150°C. benzoic acid is obtained.

m.p.	=	119°C.
mixed m.p.	=	119°C.
Yield	=	45%

Ethylbenzene requires 2 hours heating at 130-150°C. to give benzoic acid.

m.p.	=	118°C
mixed m.p.	=	115-120°C
Yield	=	75%

tert.-Butylbenzene will not oxidise under the required conditions.

Propylbenzene, after 2 hours, yields benzoic acid.

m.p.	=	116-120°C
mixed m.p.	=	118-121°C
Yield	=	85%

p-Ethyltoluene requires 2 hours to yield terephthalic

acid which sublimes. Yield = 80%. With methyl alcohol the dimethyl ester is formed, m.p. = 140°C, the quoted being 144°C.

o-Nitroethylbenzene requires 2 hours, yielding o-nitrobenzoic acid.

m.p. = 142-143°C

mixed m.p. = 143-144°C.

The yield is very good but much is lost, due to the violent opening of the tube.

p-Nitroethylbenzene in 2 hours yields p-nitrobenzoic acid in poor quantity again, due to the explosive opening of the tube.

m.p. = 236-240°C

mixed m.p. = 242°C

o-Bromotoluene gives o-bromobenzoic acid readily.

m.p. = 146°C

mixed m.p. = 146°C

Yield = 50%

m-Bromotoluene yields m-bromobenzoic acid.

m.p. = 151°C

mixed m.p. = 153°C

Yield = 66%

p-Bromotoluene yields p-bromobenzoic acid.

m.p. = 248°C

mixed m.p. = 248°C

Yield = 30%

2-4-6-Tribromotoluene does not oxidise by this method at all, the unchanged compound being obtained every time. Various conditions of temperature and time have been tried without success.

o-Chlorotoluene. yields o-chlorobenzoic acid.

m.p. = 137°C

mixed m.p. = 136°C

Yield = 10%

m-Chlorotoluene yields m-chlorobenzoic acid.

m.p. = 154°C

Yield = 20%

Titration with 0·105 N. NaOH shows the molecular weight to be 151, while molecular weight of m-chlorobenzoic acid is 156.

p-Chlorotoluene yields p-chlorobenzoic acid.

m.p. = 235°C

Yield = 60%

Methyl ester is formed by refluxing with methyl alcohol, m.p. = 41-42°C. Quoted m.p. = 44°C

Cohen and Miller (J.C.S., 1904, 85, 174) found that, in the monochlorotoluenes oxidation in sealed tubes with nitric acid, the rate of oxidation of para > ortho > meta, whereas the above method shows meta to be the intermediate one.

o-Iodotoluene oxidises with difficulty to o-iodobenzoic acid.

m.p. = 156°C

Yield = 5%

Titration with 0·106 N. NaOH shows the molecular weight to be 243 whilst that of o-iodobenzoic acid is 248.

m-Iodotoluene oxidises more readily to m-iodobenzoic acid.

m.p. = 182°C

Yield = 45%

Methyl ester formed from methyl alcohol has m.p. = 52-54°C, the quoted being 54°C.

p-Iodotoluene yields p-iodobenzoic acid.

m.p. = 259°C

Yield = 10%

Methyl ester, m.p. =111°C, prepared from methyl alcohol. Quoted m.p. = 114°C.

The oxidation of iodotoluenes with potassium permanganate is extremely difficult. They are very resistant to oxidation by any method, but the sealed tube method always yields sufficient acid for identification. The ortho compound is much more resistant than the para and meta.

Benzyl chloride readily yields benzoic acid.

m.p. = 117°C

mixed m.p. = 119°C

Yield = 90%

Benzal chloride readily yields benzoic acid.

m.p. = 118°C.

mixed m.p. = 119°C.

Yield = 66%

Benzotrichloride readily yields benzoic acid.

m.p. = 118°C.

mixed m.p. = 118°C.

Yield = 67%

o-Nitrotoluene will not yield the corresponding acid under any conditions in the sealed tube. The action must be very violent and probably spontaneous because the explosive opening of the tube renders impossible any identification.

m-Nitrotoluene yields m-nitrobenzoic acid

m.p. = 137°C.

Yield = 50%

Methyl ester, m.p. = 76°C, prepared from methyl alcohol. Quoted m.p. = 78°C.

p-Nitrotoluene yields p-nitrobenzoic acid.

m.p. = 238°C.

Yield = 60%

Methyl ester, m.p. = 94°C., prepared from methyl alcohol. Quoted m.p. = 96°C.

Cohen and Hodsman (J.C.S., 1907, 91, 970) have found that the amount of oxidation of para is

greater than meta and that the rate of ortho is least. We have found this also, so that the rate of oxidation of the nitrotoluenes is dependent on the position of the nitro group.

o-Nitrobenzyl chloride, after 2 hours, yields o-nitrobenzoic acid.

m.p. = 146°C.
mixed m.p. = 146°C.
Yield = 5%

m-Nitrobenzyl chloride yields m-nitrobenzoic acid.

m.p. = 140°C.
Yield = 45%

M.p. of methyl ester prepared from methyl alcohol = 78°C.
Quoted m.p. = 78°C.

p-Nitrobenzyl bromide yields p-nitrobenzoic acid.

m.p. = 238°C.
Yield = 90%

M.p. of methyl ester prepared from methyl alcohol = 94°.
Quoted m.p. = 96°.

p-Nitrobenzyl alcohol yields p-nitrobenzoic acid.

m.p. = 238°C.
Yield = 70%
m.p. of methyl ester = 93°C.

2-Chloro-4-nitrotoluene does not oxidise readily, the chlorine in the ortho position appearing to have a

hindering effect. Cohen and Hodsman (loc. cit.) obtained the acid by heating for 4½ hours at 123-133°C.

The Xylenes oxidise very readily and explosively. One hour at 130-150°C yields the corresponding phthalic acids in poor quantity and in every case several attempts had to be made to obtain any material, due to the tube exploding after 30 minutes heating. The reaction would appear to be spontaneous. However, a longer time at 100°C. yields the toluic acids, a reaction which is not nearly so violent.

o-Xylene, heated for 2 hours at 100°C., yields o-toluic acid.

m.p.	=	102°C.
mixed m.p.	=	103°C.
Yield	=	20%

m-Xylene, after 3 hours at 100°C., gives m-toluic acid.

m.p.	=	108°C.
mixed m.p.	=	109°C.
Yield	=	70%

p-Xylene, heated for 2 hours at 100°C., yields p-toluic acid.

m.p.	=	177°C.
Yield	=	30%

Titration with 0·1045 N. NaOH gives a molecular weight of 137 in comparison with that of 136 calculated for

p-toluic acid. Tetrahydronaphthalene, mesitylene and quinaldine do not oxidise under the required conditions.

α- and β-methylnaphthalene oxidise with difficulty to the corresponding naphthoic acids. The m.p.'s are 157°C. and 183°C., and mixed m.p.'s = 156-157°C and 182°C. respectively. The yields in both cases are 5%.

Mandelic acid readily yields benzoic acid.

m.p. = 120°C.

mixed m.p. = 121°C.

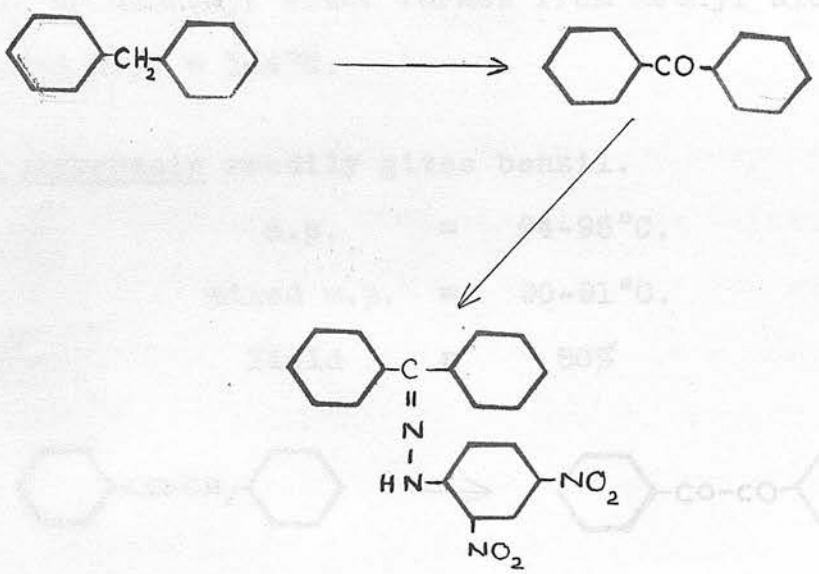
Yield = 90%

Diphenylmethane gives rise to benzophenone. An oil is formed which readily gives a 2-4-dinitrophenylhydrazone.

m.p. = 233°C.

Yield = 60% of derivative

Quoted m.p. = 238°C.



p-p'-Dimethyldiphenyl yields a pale yellow leafy solid with acidic properties and no definite melting point.

Yield = 60%

Titration with 0·106 N. NaOH shows a molecular weight of 241. p-p'-Dicarboxylicdiphenyl has a molecular weight of 242

Acetophenone oxidises violently to benzoic acid, much being lost on the opening of the tube. The yield is good.

m.p. = 121°C.

mixed m.p. = 121°C.

p-Methylacetophenone yields terephthalic acid.

Yield = 80%

M.p. of dimethyl ester formed from methyl alcohol = 139°C.
Quoted m.p. = 144°C.

Desoxybenzoin readily gives benzil.

m.p. = 94-95°C.

mixed m.p. = 90-91°C.

Yield = 80%

o-Nitrodesoxybenzoin undergoes no change. This must be due to the presence of the nitro group in the ortho position to the ketonic group.

4-Chloro-m-xylene.

Two specimens of this were used, one pure and the other containing sufficient dissolved iodine to colour it red. By varying the conditions and carrying out experiments on a larger scale, various results were obtained which are tabulated below. It was thought after the preliminary experiments that the dissolved iodine might catalyse the reaction, but further experiments disproved this. The inference from the table is that above 180°C. on the small scale the phthalic acid is obtained, and between 120°C. and 150°C. the toluic acid. One hour at 130-150°C. seems to be the most suitable for conversion into the toluic acid. At a lower temperature the reaction only goes very slowly. On the larger scale, at temperatures above 100°C., the phthalic acid is formed. The results, therefore, on the 0·5 g. and the 4 g. scale are not comparable, due to the difference in area exposed, the thickness of the respective metal tubes and the time factor with respect to the size. On a large scale it is a convenient method for the preparation of the chlorophthalic acid, and on the small, for the identification of the 4-chloro-m-xylene. The phthalic acid dimethyl ester

was prepared, m.p. = 41-42°C., and a mixed m.p. of the chlorotoluic acid with 4-chloro-3-methylbenzoic acid was 209°C. The yields in all cases varied from 65% to 80%.

Small Scale Experiments with 0·5 g.

Purity	Conditions	Acid obtained	M.p. in °C.
Pure	1 hr. at 130-150°	toluic	208
Impure	1 hr. at 130-150°	toluic	205-206
Impure	2 hr. at 130-150°	toluic	206-207
Impure	4 hr. at 130-150°	toluic	204-206
Impure	1 hr. at 180-200°	phthalic	287

Large Scale Experiments with 4 g.

Purity	Conditions	Acid obtained	M.p. in °C.
Impure	3/4 hr. at 130-135°	phthalic	287-289
Pure	3/4 hr. at 130-135°	-	-
Pure	2 hr. at 130-135°	phthalic	288-291
Impure	2 hr. at 130-135°	phthalic	290
Impure	1 hr. at 80-100°	-	-
Impure	1 hr. at 100-120°	-	-
Impure	4 hr. at 100-120°	trace toluic	208
Impure	24 hr. at 100-120°	toluic	208

The quoted melting points for 4-chloro-3-methylbenzoic acid and 4-chloroisophthalic acid are 209°C. and 294°C. respectively.

The corresponding 4-bromo-m-xylene and 4-iodo-m-xylene were now tried to find if there is any analogy between them and the chloro compound.

4-Bromo-m-xylene under normal conditions (1 hour at 130-150°C) yields 4-bromo-3-methylbenzoic acid.

m.p. = 209°C.

Yield = 40%

Titration with 0.106 N. NaOH showed the molecular weight to be 209, whilst that calculated for 4-bromo-3-methylbenzoic acid is 215. Oxidation under normal pressure with nitric acid requires 10 hours to give a 36% yield. This shows the advantage of sealed tube oxidation over that at normal pressure .

4-Iodo-m-xylene yields 4-iodo-3-methylbenzoic acid under normal conditions.

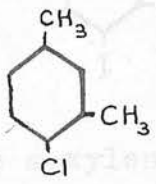
m.p. = 212°C.

Yield = 10%

Titration with 0·106 N. NaOH shows the molecular weight to be 258, that calculated for iodotoluic acid being 262. Oxidation under normal pressure requires 50 hours (Grahl, Ber., 1895, 28, 87), and after four crystallisations the melting point can be raised to 212°C. This again points out the advantages of the sealed tube method.

Preparations.

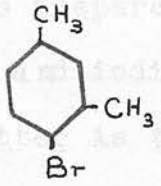
4-Chloro-m-xylene (Jacobsen, Ber., 1885, 18, 1761)



A steady current of chlorine is passed into 100 g. pure m-xylene containing 5% iodine, until the theoretical increase in weight is obtained. The solution is purified with concentrated caustic soda solution, dried over calcium chloride and distilled. The fraction boiling at 181-190°C. is collected.

Yield = 70%

4-Bromo-m-xylene (Datta, Chatterjee, J.A.C.S. 1916, 38, 2550)



20 c.c. pure m-xylene

10 c.c. conc. HNO_3

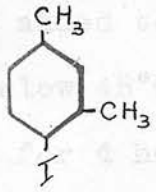
30 g. bromine

These are mixed and heated on a water-bath for 2 hours. The oil formed is separated, washed repeatedly with water, dried over calcium chloride and distilled. A colourless oil is obtained.

b.p. = 205-210°C.

Yield = 8 g. (26% theory)

4-Iodo-m-xylene (Edinger, Goldberg, Ber., 1900, 33, 2878)



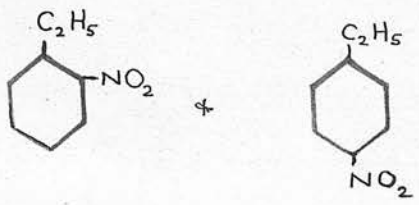
10 g. pure m-xylene dissolved in 80 c.c. benzene, 20 g. sulphur iodide and 120 c.c. nitric acid (sp. gr. = 1·34) are refluxed on a water bath for 4 hours. The benzene is distilled off and the residue heated on a water-bath till no more fumes are evolved. The oil formed is washed with water, extracted with ether, dried over calcium chloride and distilled in vacuo, when a red oil is obtained.

b.p. = 110-115°C. at 25 mm.

Yield = 15 g. (75% theory).

The sulphur iodide is prepared by dissolving equimolecular portions of sulphur and iodine in sufficient carbon disulphide. The latter is then allowed to evaporate off at room temperature. A dark grey solid remains, which is sulphur iodide, S_nI_n, as generally accepted, although some workers claim SI_6.

o- and p-Nitroethylbenzene (Schultz and Flachstander, J. prakt. Chem., 1902, 66, 162)



A mixture of 16·5 g. conc. HNO_3 and 21 g. conc. H_2SO_4 are slowly added to 20 g. ethylbenzene and stirred for 1½ hours below 45°C. The nitrous fumes are removed by heating for 4 hours on a water-bath, when a red oil is formed. This is repeatedly washed with water and moderately concentrated NaOH and steam distilled. The oil is extracted with ether, dried over calcium chloride and distilled. The fraction boiling at 135-160°C. is unchanged ethylbenzene and is discarded. The fraction boiling at 220-240°C. is collected and dried, then fractionated when the two nitroethylbenzenes are obtained.

Ortho compound: b.p. = 220-225°C.

Yield = 2 g.

Para compound: b.p. = 230-240°C. solidifying as fine orange needles.

Summary of Results.

Compound	Product - Acid except in those marked ×	Acid	
		m.p. found	m.p. quoted
Toluene	benzoic	119	121
* ethylbenzene	benzoic	118	121
*propylbenzene	benzoic	116-120	121
* ethyltoluene	terephthal ic		
* o-xylene	o-toluic	102	104
* m-xylene	m-toluic	108	109
* p-xylene	p-toluic	177	178
mesitylene	-	-	-
α-methylnaphthalene	α-naphthoic	157	160
β-methylnaphthalene	β-naphthoic	183	183
diphenylmethane	benzophenone ×	oil	48
p-p'-dimethyldiphenyl	p-p'-diphenyldicarboxy		
tetrahydronaphthalene	-	-	-
o-nitrotoluene	-	-	-
m-nitrotoluene	m-nitrobenzoic	137	140-141
p-nitrotoluene	p-nitrobenzoic	238	240
* o-nitroethylbenzene	o-nitrobenzoic	142-143	148
* p-nitroethylbenzene	p-nitrobenzoic	236-240	240
* o-nitrobenzyl chloride	o-nitrobenzoic	146	148
m-nitrobenzyl chloride	m-nitrobenzoic	140	140-141
p-nitrobenzyl bromide	p-nitrobenzoic	238	240

Summary of Results (cont.)

Compound.	Product - Acid except in those marked ×	Acid	
		m.p. found	m.p. quoted
p-nitrobenzyl alcohol	p-nitrobenzoic	238	240
o-chlorotoluene	o-chlorobenzoic	137	140
m-chlorotoluene	m-chlorobenzoic	154	154-155
p-chlorotoluene	p-chlorobenzoic	235	236
benzyl chloride	benzoic	117	121
benzal chloride	benzoic	118	121
benzotrichloride	benzoic	118	121
2-chloro-4-nitrotoluene	-	-	-
4-chloro-m-xylene	4-chloro-m-toluic	206	209
o-bromotoluene	o-bromobenzoic	146	148
m-bromotoluene	m-bromobenzoic	151	155
p-bromotoluene	p-bromobenzoic	248	251
2-4-6-tribromotoluene	-	-	-
4-bromo-m-xylene	4-bromo-m-toluic	209	209
o-iodotoluene	o-iodobenzoic	156	162
m-iodotoluene	m-iodobenzoic	182	186
p-iodotoluene	p-iodobenzoic	259	264
4-iodo-m-xylene	4-iodo-m-toluic	212	214
1-4-4'-trinitrodiphenyl-methane	-	-	-
quinaldine	-	-	-
mandelic acid	benzoic	120	121
acetophenone	benzoic	121	121

Summary of Results (cont.)

Compound	Product - Acid except in those marked ×	Acid	
		m.p. found	m.p. quoted
p-methylacetophenone	terephthalic		
desoxybenzoin	benzil ×	94-95	95
o-nitrodesoxybenzoin	-	-	-

* denotes special conditions.

Blank spaces indicate sublimation or decomposition of the product.

II. ALKYL HALIDES.

Alkyl halides react with thiourea and substituted thioureas to form the corresponding S-alkyl-isothiourea hydrohalide. These are very deliquescent solids and so are useless for identification purposes. They react readily in alcoholic solution with picric acid in alcohol to form stable picrates with good crystalline structures and melting points. The reaction depends primarily on the tautomerism of thiourea.

$$NH_2 \cdot CS \cdot NH_2 \rightleftharpoons NH_2 \cdot CSH{=}NH$$

thiourea isothiourea

$$NH_2 \cdot CSH{=}NH + RX \longrightarrow NH_2 \cdot CSR{=}NH,HX$$

$$NH_2 \cdot CSR{:}NH,HX + (NO_2)_3 \cdot C_6H_2 \cdot OH \longrightarrow (NH_2 \cdot CSR{:}NH)((NO_2)_3 \cdot C_6H_2 \cdot OH) + HX$$

R = alkyl group
X = halide group

We thought that it was probable that phenylthiourea (Bertram, Ber., 1892, 25, 49) might give better crystalline derivatives than the unsubstituted thiourea. Equal quantities of alkyl halide and phenylthiourea, $C_6H_5 \cdot NH \cdot CS \cdot NH_2$ (about 0·2 g.), are heated with 2 c.c. alcohol for 5 minutes. This is cooled and 2 c.c. of aqueous sodium carbonate solution added, when a white solid separates along with an oil.

The solid is filtered off; the oil separated, dissolved in alcohol and added to a saturated alcoholic solution of picric acid. On cooling, the crystalline picrate separates. It is purified by crystallisation from alcohol. This method is quite suitable for the normal chain iodides and bromides, but useless for the branched chain compounds and the alkyl chlorides. The iodides react much more readily than the bromides and actually do not require the addition of alkali. The branched chain compounds, like isobutyl iodide, sec-butyl iodide, etc., were refluxed for 3 hours with the phenylthiourea, but without any positive results, except in the case of cyclohexyl bromide. The results obtained are tabulated below along with the analysis figures. The nitrogen determinations for every new compound have been done by Pregl's modification of the Micro Dumas method ourselves.

Note:- In this and subsequent tables, blank spaces in the analysis columns indicate that the compound has already been described in the literature. Dashes - in any column indicate that the results obtained in these cases are negative.

S-Alkyl-N-Phenylisothiourea Picrates.

Alkyl Halide	Picrate			
	m.p. in °C.	Crystalline Appearance.	%N.Calc.	%N.Found
Methyl iodide	175	Yellow plates		
ethyl iodide	196	yellow needles		
propyl iodide	167	yellow needles	16·6	16·6
propyl bromide	166	yellow needles	16·6	16·6
isopropyl iodide	-	-	-	-
butyl iodide	143	square yellow plates	16·0	16·1
butyl bromide	144	square yellow plates	16·0	16·1
isobutyl iodide	-	-	-	-
sec-butyl iodide	-	-	-	-
amyl iodide	141	pale yellow needles	15·5	15·8
isoamyl iodide	152	feathery yellow needles	15·5	15·8
ethylene dibromide	201	pale yellow needles	17·5	17·4
cyclohexyl bromide	176	pale yellow needles	15·1	15·4
benzyl chloride	137	pale yellow needles	14·9	14·5
n-hexyl bromide	-	-	-	-
propyl chloride	-	-	-	-
amyl chloride	-	-	-	-
tert-amyl bromide	-	-	-	-

Thiourea itself was now tried and the procedure in this case found to be much simpler. About 0·2 g. finely-powdered thiourea and an equal quantity of alkyl halide are heated with 1-2 c.c. alcohol in a small tube for 1-2 minutes. A saturated alcoholic solution of picric acid is added and, on cooling, the picrate separates out. It is purified by crystallisation from boiling alcohol till a constant, sharp melting point is obtained. The picrate of S-methylisothiourea has been formed by Wheeler and Bristol (Amer. J., 1905, 33, 441). Werner has found that the reaction applies also to allyl bromide (J.C.S., 1890, 57, 298) and to ethyl iodide (J.C.S., 1919, 115, 1172). We found it to be most satisfactory with all the alkyl iodides and bromides which were tried, except with tert-amyl bromide. Isopropyl iodide and sec-butyl iodide, etc., reacted very readily. The reagent is, however, not suitable for chlorides, several of which have been tried.

The picrates formed with the bromides and iodides have beautiful crystalline structures which are distinct in nearly every case. Because of this, micro-photographs have been taken of all the distinct types of crystals, to show their characteristic crystalline forms and to aid in identification. The apparatus used was a Leitz photomicrographic reflex camera fixed to the eyepiece of an ordinary microscope. It required 4½ cm.

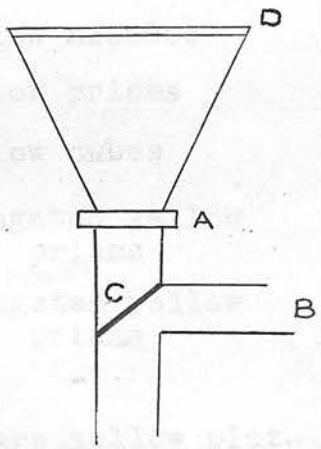
by 6 cm. Ilford Special Rapid backed Panchromatic plates. A magnification of 50 diameters, calibrated against a standard screw, was used. Since the crystals are all of a yellow colour, a blue contrast light filter was used at the source of illumination, which was a 100 watt opal light bulb. The plates were desensitized and developed by the Watkins Factorial method.

A is shutter

B is eyepiece

C is movable mirror

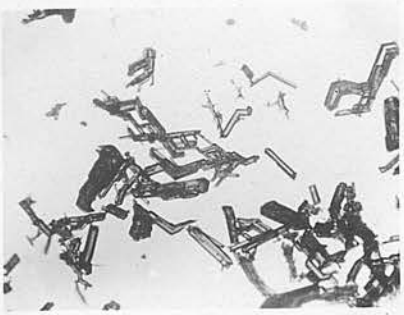
D is plate



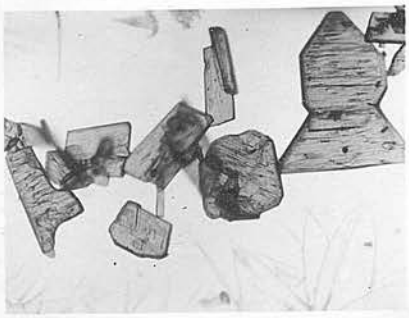
The whole diagram represents that substituted for the microscope eyepiece.

S-Alkylisothiourea Picrate.

Alkyl halide.	Picrate.			
	m.p. in °C.	Crystalline Appearance.	%N.Calc.	%N.found
Methyl iodide	224	Yellow prisms		
ethyl iodide	188	square yellow plates		
propyl iodide	181	rectangular yellow plates	20·2	20·6
isopropyl iodide	148	triangular yellow plates	20·2	20·4
butyl iodide	180	yellow needles	19·4	19·7
isobutyl iodide	174	yellow prisms	19·4	19·7
sec-butyl iodide	190	yellow cubes	19·4	19·5
amyl iodide	154	elongated yellow prisms	18·7	18·8
isoamyl iodide	179	elongated yellow prisms	18·7	18·8
cyclohexyl iodide	-	-	-	-
ethyl bromide	188	square yellow plates		
propyl bromide	180	rectangular yellow plates	20·2	20·6
isopropyl bromide	148	triangular yellow plates	20·2	20·6
butyl bromide	180	yellow needles	19·4	19·7
amyl bromide	154	elongated yellow prisms	18·7	18·8
isoamyl bromide	179	elongated yellow prisms	18·7	18·8
sec-amyl bromide	143	orange plates	18·7	18·9
tert-amyl bromide	-	-	-	-
n-hexyl bromide	157	yellow plates	18·0	18·3
cyclohexyl bromide	-	-	-	-
ethylene dibromide	270	small yellow crystals	24·1	23·9
allyl bromide	155	square orange prisms		
benzyl chloride	188	yellow needles	17·7	17·6



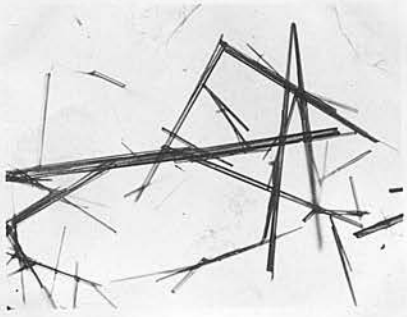
Methyl.



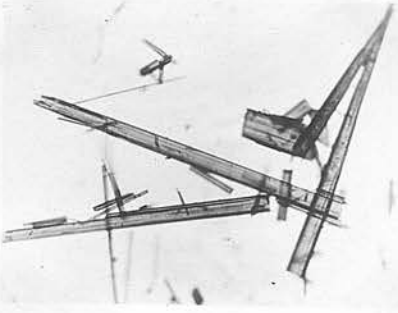
Ethyl.

Propyl.

Isopropyl.

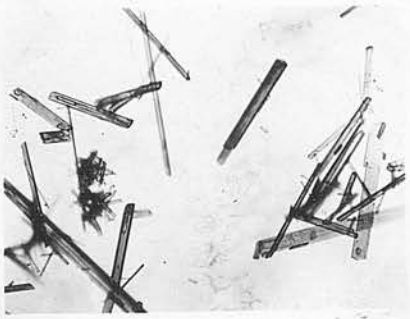


Butyl.

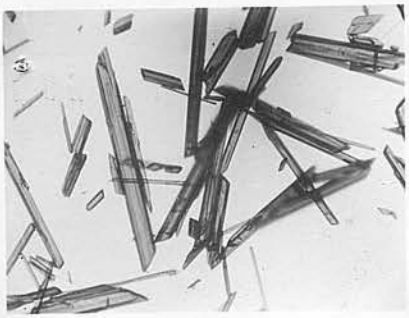


Isobutyl.

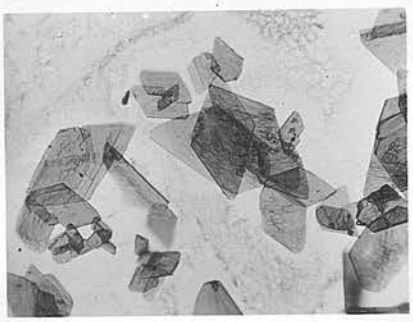
sec-Butyl.



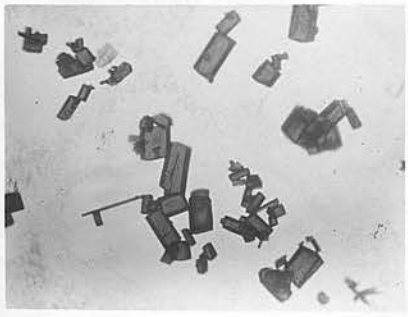
Amyl.



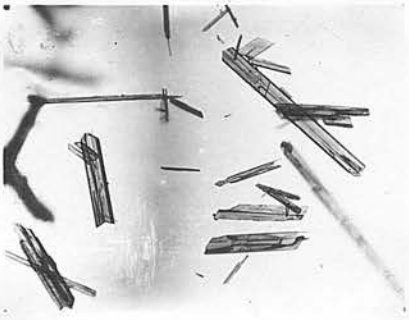
Isoamyl.



Hexyl.



Allyl.



Benzyl.

From the table it is seen that the derivatives of some of the neighbouring members of the series have melting points which are rather close together. For example, S-propylisothiourea picrate melts at 181°C, whilst that of butyl melts at 180°C and of isoamyl at 179°C. For identification purposes these are too close together but by taking several other factors into consideration a distinction can easily be made. There are four points to be considered:

1) The melting point narrows the choice to two or three compounds.

2) The boiling point of the original halide.

3) The crystalline appearance under the microscope. For example, in the case quoted above, the propyl compound has the appearance of plates under the microscope, the butyl that of needles, and the isoamyl of elongated prisms. By comparing these with the photographs a fairly definite decision can be made.

4) A mixed melting point of the picrate with a standard sample. If the melting point is depressed, then the picrate is different, but if it remains the same then the same substances have been mixed.

Thus the alkyl group of the alkyl halide can definitely be identified and proved in a very short

time by a very simple process. It is much to be preferred to the anilides and α-naphthalides prepared by the Grignard process, and to the phthalimide process of Sah and Ma (Ber., 1932, 65, 1630) which requires at least 10 hours for completion. The iodo and bromo groups can be distinguished by the chloroform and chlorine water test. A little of the original halide is fused with sodium, poured into water, chlorine water added, then chloroform drop by drop. On shaking, an orange colour is produced by bromine and a deep red by iodine.

No derivatives could be obtained with the tertiary compounds, cyclohexyl iodide or cyclohexyl bromide. All other compounds tried were successful.

Preparations.

Phenylthiourea $C_6H_5 \cdot NH \cdot CS \cdot NH_2$ (De Clermont, Ber., 1876, 9, 446)

52 g. aniline hydrochloride

30 g. ammonium thiocyanate

82 g. water

These are heated at 100 °C for 10 hours, then evaporated to dryness and heated again at 100 °C for 4 hours. The product is ground up in a mortar with cold water to remove ammonium chloride. The residue is crystallised from boiling alcohol after purification

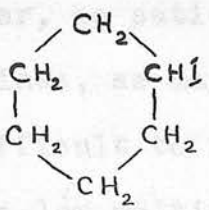
with animal charcoal. White prisms, m.p. = 140-145°C, are formed. After another crystallisation white prisms are obtained.

m.p. = 154°C.

quoted m.p. = 154°C.

yield = 20 g. (33% theory when pure)

Cyclohexyl Iodide. (Finkelstein, Ber., 1910, 43, 1528)



15 g. cyclohexyl bromide are boiled for 1 hour with 100 c.c. 15% solution of sodium iodide in acetone. About 30 c.c. acetone are distilled off and the remainder poured into water, when an oil separates. This latter is shaken with mercury to remove free iodine, dried over calcium chloride and distilled in vacuo.

b.p. = 60-65°C. at 10 mm.

yield = 9 g. (48% theory)

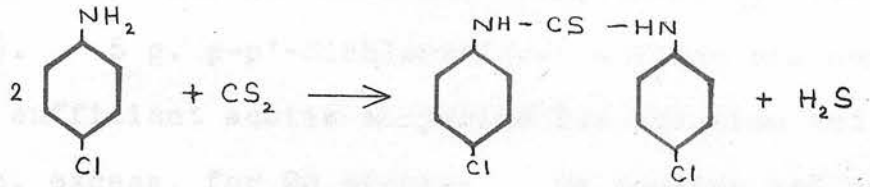
III. ALIPHATIC AMINES.

Substituted Phenylisothiocyanates as Reagents for Aliphatic Amines.

One of the most suitable reagents for characterising primary and secondary amines is phenylisothiocyanate. It is easily prepared and readily yields crystalline derivatives with aromatic amines. It is not, however, so satisfactory for identifying the aliphatic amines, as many of the resultant thioureas are difficult to obtain in the crystalline state and possess low melting points. In an effort to obtain a more suitable reagent for identifying amines in alcoholic or aqueous solution we have tried various substituted phenylisothiocyanates. The presence of substituents in the benzene ring often raises the melting point and on this assumption we used the p-chloro, m-nitro, p-methyl, p-phenyl, phenylisothiocyanates and the β-naphthylisothiocyanate

p-p'-Dichlorthiocarbanilide. (Losanitsch, Ber., 1872, 5, 156.)

The p-chlorophenylisothiocyanate is prepared from the thiocarbanilide which is obtained from p-chloroaniline.



20 g. p-chloraniline

30 g. absolute alcohol

30 g. carbon disulphide.

These are refluxed on a water-bath for 20 hours. After distilling off excess carbon disulphide and alcohol, the residue is crystallised from alcohol. White needles are formed.

m.p. = 167°C.

yield = 14 g. (67% theory)

By refluxing for only 5 hours a 22% yield is obtained.

p-Chlorophenylisothiocyanate.

Several methods have been tried for this conversion. The thiocarbanilide was first boiled up with five times its weight in conc. HCl and enough absolute alcohol to effect solution, for 4 hours (Cohen's Practical Organic Chemistry, p. 181). On extraction white needles, m.p. = 45°C. and a yield of 5% were obtained.

The better method was found to be that using acetic anhydride (Steudemann, Ber., 1883, 16, 549, 2334). 5 g. p-p'-dichlorthiocarbanilide are boiled with sufficient acetic anhydride for solution and 1 or 2 c.c. excess, for 20 minutes. On cooling and pouring into water, an oil forms which solidifies on cooling in ice. This is filtered, washed free from acetic anhydride with water and crystallised from glacial acetic acid, when white needles separate.

m.p. = 44°C.

yield = 5·2 g. (91% theory)

The method used for the preparation of a derivative of an aliphatic amine is very simple. Approximately 0·2 g. of reagent is heated in a small test tube with 0·2 g. amine for several seconds. 2 c.c. of 50% alcohol are then added. On cooling, the derivative separates out as a crystalline solid. This is crystallised from 50% alcohol till a constant, sharp melting point is obtained. The details in the preparation of the sec-butylamine derivative of p-chlorphenylisothiocyanate are given here as a typical example of the use of the isothiocyanates.

0·2 g. of sec-butylamine and of p-chlorphenylisothiocyanate are heated for about 10 secs. 2 c.c. 50% alcohol are added and, on cooling, a white solid, m.p. = 96-98°C., is formed.

Crystallised from 50% alcohol - white needles, m.p. = 109-111°C.

" " " " white needles, m.p. = 114-115°C.

" " " " white needles, m.p. = 114-115°C.

$$(sec)C_4H_9\cdot NH_2 + Cl\cdot C_6H_4\cdot NCS \longrightarrow Cl\cdot C_6H_4\cdot \underset{H}{N} - \underset{NH\cdot C_4H_9(sec)}{C} = S$$

The melting points along with the crystalline structure and analysis figures, determined by the Micro Dumas method, are tabulated below. Methylamine, ethylamine and dimethylamine are all used in 33% alcoholic solutions. The crystalline structures noted throughout are those under the microscope.

p-Chlorphenylisothiocyanate.

Amine	Derivative			
	m.p. in °C.	Crystalline Appearance	%N.Calc.	%N. found
Methyl	140	white needles	13·9	13·9
ethyl	107	white needles	13·0	13·2
propyl	109	white needles	12·3	12·2
butyl	112-113	white needles	11·6	11·4
isobutyl	120	white needles	11·6	11·3
sec-butyl	114-115	white needles	11·6	11·9
amyl	93	transparent plates	10·9	10·8
isoamyl	118	white needles	10·9	10·7
heptyl	83	lustrous white plates	9·8	10·1
octyl	59	pinkish-white needles	9·4	9·3
dimethyl	156	white needles	13·3	13·1
diethyl	60-61	white needles	11·6	11·3
dipropyl	111	white needles	10·4	10·3
di-isobutyl	123	white needles	9·4	9·6
diamyl	93	white needles	8·6	8·5
benzyl	125	white needles	10·1	10·4
cyclohexyl	176	white needles	10·4	10·4
bornyl	159-160	brownish-white needles	8·7	8·7
camphyl	121	lustrous flat plates	8·7	8·9
ethylene diamine	201	leaf-shaped white plates	18·3	17·9

Sah and Lei (loc. cit. p. 8) having used m-nitrophenylisothiocyanate as a reagent for aromatic amines, we decided to try it for aliphatic amines.

m-m'-Dinitrophenylisothiocyanate. (Fry., J.A.C.S., 1913, 35, 1544)

In this method pyridine and iodine are added to remove the H_2S formed and thus prevent the reverse reaction.

$$2R{\cdot}NH_2 + CS_2 \longrightarrow (R{\cdot}NH)_2CS + H_2S$$

$$H_2S + I_2 \longrightarrow 2HI + S$$

$$HI + C_5H_5N \longrightarrow C_5H_5N, HI$$

This latter, pyridinium iodide, is insoluble in CS_2 and thus the H_2S is completely removed from the reaction.

27 g. m-nitraniline

30 g. pyridine

350 c.c. carbon disulphide

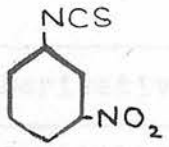
The nitraniline and pyridine are dissolved in the CS_2 and refluxed with 25 g. iodine in 150 c.c. CS_2 for 3 hours. Excess CS_2 is removed by distillation, pyridine by steam distillation, and pyridinium iodide by boiling with dilute HCl. After filtering, sulphur is removed by fractional crystallisation from alcohol, when pale yellow needles are formed.

m.p. = 168-171°C.

quoted m.p. = 160-161°C.

yield = 16 g. (54% theory)

m-Nitrophenylisothiocyanate. (Steudemann, Ber., 1883, 16, 2334)



5 g. of the thiocarbanilide are boiled with excess acetic anhydride for about 3 minutes, cooled and poured into water, when the isothiocyanate separates as pale brown needles. These are filtered, thoroughly washed with water and crystallised from glacial acetic acid. Fawn-coloured needles are formed, m.p. = 54-60°C. The melting point cannot be obtained sharp. The range seems to be characteristic of the compound.

Yield = 4 g. (94% theory)

Derivatives with amines are prepared as for the chloro compound and results are tabulated below along with the analysis results.

m-Nitrophenylisothiocyanate.

Amine	Derivatives			
	m.p. in °C.	Crystalline Appearance	%N.Calc.	%N. found
Methyl	155	fawn needles	19·9	19·7
ethyl	144	fawn needles	18·7	19·0
propyl	104	almost white needles	17·6	17·8
butyl	93	fine yellow needles	16·6	16·5
isobutyl	90	flat yellow plates	16·6	16·7
amyl	66	yellow needles	15·7	15·9
isoamyl	85	yellow prisms	15·7	15·6
heptyl	-	oily yellow plates	-	-
dimethyl	-	-	-	-
diethyl	40	oily solid	-	-
dipropyl	-	-	-	-
di-isobutyl	-	-	-	-
diamyl	-	-	-	-
benzyl	147	pale yellow needles	14·6	14·6
cyclohexyl	140	yellow plates	15·1	15·1
bornyl	-	oil	-	-
camphyl	-	oil	-	-
ethylene diamine.	142	yellow needles		

From the results, we see that m-nitrophenylisothiocyanate is of little use as a reagent. The melting points of the derivatives are lower than those of the unsubstituted phenylisothiocyanate derivatives, whilst the solids obtained are very difficult to isolate and so do not adhere to the required conditions. Probably the fact that this compound is not a good reagent is due to the unsymmetrical nature of the molecule. Unfortunately the symmetrical p-nitrophenylisothiocyanate cannot be prepared from p-nitraniline and carbon disulphide (Fry, J.A.C.S., 1913, 35, 1544). We attempted the preparation with the same results as Fry. The reagent can be prepared by means of thiophosgene but this is a method, tedious and costly, for a reagent which should be easily prepared without expense. An attempt was made to prepare 3:5-dinitro-4-methylphenylisothiocyanate by reduction of 2:4:6-trinitrotoluene to 3:5-dinitro-4-methylaniline (Holleman, Böeseken, Rec. Trav. Chim., 1897, 16, 425). This was then transformed into the thiocarbanilide and isothiocyanate by the methods used for the m-nitro compound. The yields throughout the preparation were very poor and a derivative prepared with n-butylamine showed this reagent to be of little value.

An attempt was made to prepare 3:5-dinitroaniline from 3:5-dinitrobenzoic acid with sodium azide (Oesterlin, Zeit. angew. Chem., 1932, 45, 536). The

dinitrobenzoic acid, however, was insoluble in the required amount of sulphuric acid and no positive results could be obtained although various modifications were made.

p-p'-Dimethylthiocarbanilide, $CH_3 \cdot C_6H_4 \cdot NH.CS \cdot NH \cdot C_6H_4CH_3$

11 g. p-toluidine

16 g. pyridine

200 c.c. carbon disulphide

When dissolved, these are refluxed with 13 g. iodine in 100 c.c. CS_2 for 4½ hours. Excess CS_2, pyridine, pyridinium iodide and sulphur are removed, and the product is crystallised from alcohol. White needles are formed.

m.p. = 178-180°C.

yield = 11 g. (78% theory with 4½ hours)

6 g. (45% theory with 2 hours)

p-Methylphenylisothiocyanate.

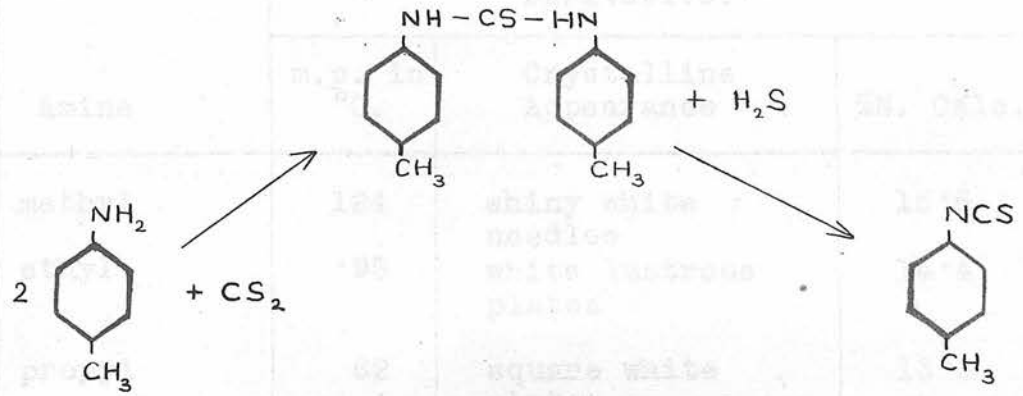
5 g. thiocarbanilide are refluxed with excess acetic anhydride for 15 minutes, cooled and poured into water, when an oily solid separates. On distillation in vacuo pure white needles are obtained.

m.p. = 26°C.

b.p. = 114°C. at 30 mm.

yield = 5 g. (88% theory)

This is in agreement with the literature although the method is different.



p-Tolylisothiocyanate has been used by Whitmore and Otterbacher (J.A.C.S., 1929, 51, 1909) for identifying aromatic amines yielding good results. We have prepared derivatives with aliphatic amines in the same way as before. These derivatives are rather slow to separate from the mother liquor but have beautiful crystalline structures. The melting points are, in general, rather lower than those of the derivatives with p-chlorphenylisothiocyanate and practically the same as those of the unsubstituted reagent, for primary amines. With ethylene diamine and cyclohexylamine, however, derivatives with reasonable melting points are formed, whereas with phenylisothiocyanate only oils are obtained. The results and analysis figures are tabulated below.

p-Methylphenylisothiocyanate.

Amine	Derivative.			
	m.p. in °C.	Crystalline Appearance	%N. Calc.	%N.found
methyl	124	shiny white needles	15·6	15·6
ethyl	95	white lustrous plates	14·4	14·3
propyl	62	square white plates	13·3	13·2
butyl	66	feathery white needles	12·5	12·3
isobutyl	86	white needles	12·5	12·5
amyl	177	white needles	11·8	11·7
isoamyl	67	square white plates	11·8	11·7
heptyl	83	white needles	10·6	10·7
octyl	-	-	-	-
dimethyl	172	feathery white needles	14·4	14·2
diethyl	74	square white plates	12·5	12·0
dipropyl	83	white needles	11·2	11·3
di-isobutyl	93	white needles	10·1	10·3
diamyl	90-91	white needles	9·2	9·3
benzyl	118	square white lustrous plates	10·9	10·6
cyclohexyl	112	white needles	11·2	11·2
bornyl	29	white needles	9·2	9·5
camphyl	108-109	yellowish-white needles	9·3	9·2
ethylene diamine	181	yellow crystalline solid	20·0	20·0

p-p'-Diphenylthiocarbanilide $(C_6H_5 \cdot C_6H_4 \cdot NH)_2CS$

17·4 g. p-aminodiphenyl

16 g. pyridine

200 c.c. carbon disulphide

These are refluxed with 13 g. iodine in 100 c.c. CS_2 for 5 to 6 hours. Excess CS_2, pyridine, pyridinium iodide and sulphur are removed as in the previous preparations. The product is boiled up with alcohol in which it is only very sparingly soluble, to remove any impurities. As a result, an almost white amorphous solid is formed, m.p. = 233-235°C. This is insoluble in ligroin, chloroform, acetone, benzene, and only very sparingly soluble in alcohol and glacial acetic acid. It has not been prepared before but there is little doubt as to its being p-p'-diphenylthiocarbanilide because of its easy conversion into the isothiocyanate and the corresponding formation of derivatives with amines.

Yield = 19 g. (97% theory)

Analyses.

	Calculated	Found	
C	78·9%	78·8%	
H	5·3%	5·6%	(Weiler)
S	8·4%	5·97%	
N	7·33%	7·37%	(Micro Dumas)

Although there is a large discrepancy in the sulphur

analysis, the compound is without doubt diphenylthiocarbanilide.

p-Diphenylisothiocyanate $C_6H_5 \cdot C_6H_4 \cdot NCS$

5 g. of the thiocarbanilide is boiled with excess acetic anhydride for 10 minutes. A reddish-brown solution is formed which is cooled and poured into water, when an oil separates, solidifying on standing. A brown solid is formed which on crystallisation from glacial acetic acid yields brown needles, m.p. = 66-68°C. This was repeated several times using animal charcoal for purification, but no further purity could be obtained. However, on crystallising from alcohol, pure white needles are obtained.

m.p. = 70°C.

yield = 5 g. (89% theory)

Analyses:

	Calculated	Found	
C	73·9%	73·4%	
H	4·3%	4·6%	(Weiler)
S	15·2%	14·2%	
N	6·64%	6·67%	(Micro Dumas)

Derivatives with amines are made in the same manner as before. The melting points of the resulting compounds are well above those of the p-chlor derivatives. The derivatives separate rapidly but do not have good crystalline structures, which is a great disadvantage.

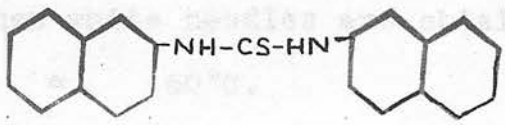
In some cases they appear as amorphous powders and only under the microscope can the crystalline structure be ascertained. It is a more expensive reagent to prepare, the p-aminodiphenyl being more difficult to obtain than p-chloraniline. The melting points of neighbouring members of the series do not differ very greatly.

p-Diphenylisothiocyanate.

Amines	Derivatives			
	m.p. in °C.	Crystalline Appearance	%N.calc.	%N.found
methyl	142	cream needles	11·6	11·6
ethyl	165	feathery white needles	10·9	10·9
propyl	156	feathery white needles	10·4	10·2
butyl	155	white needles	9·9	9·8
isobutyl	157	shiny white needles	9·9	10·0
amyl	147	white needles	9·4	9·3
isoamyl	130	white needles	9·4	9·6
heptyl	149	white needles	8·6	8·7
dimethyl	225	white prisms	10·9	11·3
diethyl	114	white needles	9·9	9·8
dipropyl	116-117	white needles	9·0	8·9
di-isobutyl	160	shiny white needles	8·5	8·5
diamyl	118	fine white needles	7·6	7·7
benzyl	147	white needles	8·8	9·0
cyclohexyl	180	shiny white plates	9·0	9·3
bornyl	167	white needles	7·7	7·8
camphyl	138	white needles	7·7	7·6
ethylene diamine	237	white solid	15·5	15·3

Since Wirtel and French (J.A.C.S., 1926, 48, 1736) used α-naphthylisothiocyanate as a reagent for alcohols and amines, we now tried β-naphthylisothiocyanate in the hope that it would prove to be the ideal reagent for amines. The methods used, with β-naphthylamine as starting material, are similar to those used for the m-nitro, etc. phenylisothiocyanates but are new for the preparation of the dinaphthylthiourea and the isothiocyanate.

β-β'-Dinaphthylthiourea



28 g. β-naphthylamine

30 g. pyridine

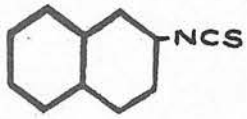
350 c.c. carbon disulphide

These are refluxed for 5 hours with 25 g. iodine in 100 c.c. CS_2. Excess CS_2, pyridine, pyridinium iodide and sulphur are removed as before (p. 52). On attempting to crystallise the resulting solid from glacial acetic acid, a white solid, m.p. = 190-200°C., is obtained. After two crystallisations from alcohol, however, white plates, m.p. = 203°C., are obtained, the quoted being 203°C. Nitrobenzene is quoted in the literature as the best crystallising agent, but alcohol

is just as efficient.

Yield = 27 g. (80% theory)

β-Naphthylisothiocyanate.



5 g. of the dinaphthylthiourea are boiled for about 15 minutes with excess acetic anhydride. On cooling and pouring into water, a white solid is obtained. This is purified by boiling with alcohol and animal charcoal, when white needles are obtained.

m.p.	=	60°C.
quoted m.p.	=	62°C.
yield	=	2·5 g. (46% theory)

The derivatives with amines are made in the same way as previously. These derivatives separate readily from solution with a beautiful crystalline structure. They have melting points between those of the p-chlorphenyl and diphenylisothiocyanate derivatives. The melting points of neighbouring members of the series and also those of isomers are considerably different, this being an advantage over the diphenyl. After two crystallisations, the melting points are sharp and constant, showing that pure derivatives result. The results are tabulated below with the analysis figures. In cases marked with an asterisk the analyses were done

by Weiler of Oxford but in the others were done by ourselves (Micro Dumas).

β-Naphthylisothiocyanate.

Amine	Derivatives. m.p. in °C.	Crystalline Appearance	%N.calc.	%N.found
* methyl	127	white needles	13·0	12·8
* ethyl	142	white needles	12·2	12·2
propyl	114	shiny white plates	11·5	11·5
butyl	119	white needles	10·9	11·2
isobutyl	137	shiny white plates	10·9	11·2
amyl	114	white prisms	10·3	10·6
isoamyl	116	white prisms	10·3	10·1
heptyl	115	white prisms	9·3	9·7
* dimethyl	173	white needles	11·4	12·2
* diethyl	90	white needles	10·9	10·7
dipropyl	109	feathery white needles	9·8	9·9
di-isobutyl	136	white needles	8·9	9·2
diamyl	126	feathery white needles	6·5	6·6
benzyl	173	white plates	9·6	9·7
cyclohexyl	172	white needles	9·9	10·1
* camphyl	127	white needles	8·6	8·3
ethylene diamine	223	white needles	17·1	17·4

Comparative Table.

Amine.	M.p. of Derivatives of Substituted Phenylisothiocyanates.					
	unsub.	p-chloro	m-nitro	p-methyl	p-phenyl	β-naphthyl
methyl	151	140	155	124	142	127
ethyl	99	107	144	95	165	142
propyl	63	109	104	62	156	114
butyl	65	112-113	92	66	155	119
iso-butyl	82	120	89-90	86	157	137
sec.butyl	101	114-115				
amyl	69	93	65-66	177	147	114
isoamyl	102	118	85	67	130	116
heptyl	75	83	oily	83	149	115
octyl	-	59	-	-	-	
dimethyl	135	156	oil	172	225	173
diethyl	34	60-61	-	74	114	90
dipropyl	69	111	-	83	116-117	109
di-isobutyl	113	123	-	93	160	136
diamyl	72	93	-	90-91	118	126
benzyl	156	125	147	118	142	173
cyclohexyl	-	176	140	112	180	172
bornyl	-	160	-	26	167	
camphyl	125·5	121	-	108-109	138	127
ethylene diamine	-	201	142	181	237	223

Blank spaces indicate that no more of that particular amine could be obtained.

Relative Merits of the Various Reagents.

From the comparative table of the melting points of the amine derivatives of phenylisothiocyanate and the various substituted phenylisothiocyanates, the merits of the various reagents over the unsubstituted can be noted. From all the foregoing results it is seen that the β-naphthylisothiocyanate has many advantages over the others. The m-nitro derivatives can be dispensed with since they are no improvement on the phenylisothiocyanate derivatives. The methyl derivatives have melting points which in many cases are rather low, and as we want a reagent which gives good derivatives with every member of the series, this is useless. The crystalline structure of these derivatives is remarkably good but they are rather slow to separate from solution. The diphenylisothiocyanate has two disadvantages. The crystalline structure is very poor and the melting points of adjacent members of the series and of isomers are rather close together. For example, n-butyl and isobutyl only differ by one degree; propyl differs from butyl by one and from ethyl by five degrees. Diphenyl derivatives have the advantage that they separate rapidly and have good melting points.

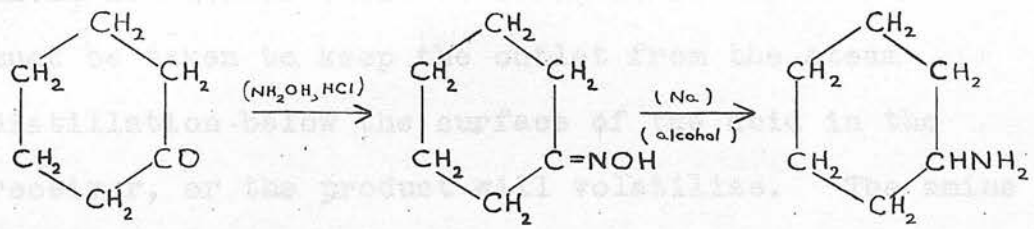
We are now left with p-chlor and β-naphthyl derivatives to choose from. The main disadvantage

of the former is the slowness of separation of the crystals. The solids come down in an amorphous form, but on standing, crystals appear. On the whole, the melting points of the β-naphthyl derivatives are higher than those of the chloro compounds, and the difference between adjacent members more marked. The derivatives also separate very readily in good crystals. We may, therefore, choose the β-naphthylisothiocyanate as the most suitable reagent. It can be prepared in good yield from β-naphthylamine and the cost of preparation is reasonably low.

We have here a reagent for primary and secondary aliphatic amines which has many points in its favour over those previously used. The operation can be carried through in a very short time without any special precautions and, as the reagent can be prepared in a large quantity at a time, requires very little preparative work. The yields in every case are very good and 0·2 g. amine yields sufficient material to permit several crystallisations. It is particularly useful in the case of diethylamine which is obtained as a byproduct in many industrial manufactures. The derivative with phenylisothiocyanate melts at 34°C., whilst that with the β-naphthyl compound melts at 90°C. Any of the amines can be detected in dilute alcoholic or aqueous solution, about 10%, so that it will be very useful for the detection of amines.

Most of the amines used were obtained commercially but several had to be prepared in the laboratory, and an account of their methods of preparation are given below.

Cyclohexylamine from cyclohexanone.



Preparation of cyclohexanone oxime.

10 g. cyclohexanone and 10 g. anhydrous sodium carbonate in 35 c.c. water are chilled in ice and stirred. To this is added slowly, with stirring, 7·1 g. hydroxylamine hydrochloride in 15 c.c. water. This is allowed to stand for 1 hour, when oxime is filtered, washed with ice water twice and crystallised from ligroin, using 4 c.c. per g. of oxime. White needles are formed.

m.p. = 86°C.

yield = 8 g. (72% theory, purified)

Cyclohexylamine. (Organic Synthesis, 11, 58,1929)

8 g. oxime are dissolved in a 500 c.c.

bolthead in 120 c.c. dehydrated absolute alcohol (Organic Synthesis, 7, 37, 1929). This is heated to boiling on a steam-bath which is then removed, and 12 g. sodium slowly introduced through the condenser at such a rate as to maintain the temperature and not to lose any alcohol. On cooling, 150 c.c. water are added, and the whole steam distilled in 20 c.c. 6 N.HCl until no further basic reaction is obtained. Care must be taken to keep the outlet from the steam distillation below the surface of the acid in the receiver, or the product will volatilise. The amine hydrochloride is obtained by evaporation to dryness and drying at 100°C.

Yield = 6·5 g. (72% theory)

This is dissolved in 10 c.c. water and made alkaline with conc. NaOH solution. The free amine is extracted with ether, dried over sodium, the ether removed, and then fractionated. The fraction boiling at 130-132°C. is pure cyclohexylamine, the boiling point being that quoted in the literature.

Yield = 2 g. (45% theory).

An attempt was made to prepare sec-butylamine from methyl ethyl ketone by a similar method. The oxime and amine hydrochloride were obtained, but the amine was lost, due to its solubility in water and its low boiling point.

n-Heptylamine. (Oesterlin, Zeit. angew. Chem., 1932, 45, 536).

$$C_7H_{15}.COOH + N_3H \longrightarrow C_7H_{15}NH_2 + CO_2 + N_2$$

25 g. caprylic acid

30 c.c. conc. sulphuric acid

100 c.c. chloroform

The caprylic acid is dissolved in the sulphuric acid, and the chloroform added. 13·5 g. sodium azide is now added in small portions, with occasional stirring, and keeping the temperature below 40°C. This is left overnight, the chloroform layer removed, and the aqueous layer neutralised with solid potassium hydroxide until no more potassium sulphate precipitates. The amine is extracted with ether, dried over KOH, the ether removed, and distilled. A clear, colourless liquid is obtained.

b.p. = 144-145°C.

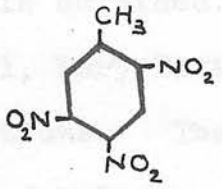
yield = 2 g. (10% theory)

n-Octylamine $C_8H_{17}NH_2$

The method is the same as that for n-heptylamine, starting with 20 g. pelargonic acid in 40 c.c. conc. H_2SO_4 and 80 c.c. chloroform. 9·5 g. sodium azide is added and after extraction, 1 g. of amine, b.p. = 160-170°C., is obtained. The reaction does

not go so well and the method had to be abandoned because of a recent explosion with sodium azide in the Imperial Chemical Industries Laboratories. It was suggested by the investigators of this accident that no more work should be done with this particular reagent by research students. For this reason we had to abandon this preparation and also a similar one for sec-butylamine , and this accounts for blank spaces in the tables.

Derivatives of Aliphatic Amines with 2:4:5-Trinitrotoluene.



Barger and Tutin (Biochem. J., 1918, 12, 402) used 2:4:5-trinitrotoluene as a reagent for certain amino acids. The 5-nitro group is activated by nitro groups in the ortho and para positions to it, and hence reacts with amines and amino acids. The nitro group is completely removed and the amine enters its position. The primary amine or amino acid in alcohol reacts at once with the trinitrotoluene with the immediate separation of the 5-substituted 2:4-dinitrotoluene. With methylamine, for example, we get:

Owing to the great insolubility of the derivatives it is very useful for the detection of small quantities of primary amines. The reagent was kindly prepared by Mr G. Thomson in the Organic Laboratory.

0·05 - 0·1 g. of trinitrotoluene are dissolved in 1 c.c. alcohol, and 3-4 drops of the amine are added. On shaking, the derivative separates out.

It is purified by crystallisation from alcohol. In every case yellow or orange crystalline solids are obtained. Purification is carried out until a constant, sharp melting point is obtained. Owing to the slight solubility in alcohol, very little is lost through repeated crystallisations. The melting points, etc. obtained are tabulated below.

Amine	Derivative			
	m.p. in °C.	Crystalline Appearance.	% N. Calc.	% N. Found.
methyl	174	yellow needles		
ethyl	126	yellow needles	18·7	18·7
propyl	101	yellow needles	17·6	17·4
butyl	96	yellow needles	16·6	16·5
isobutyl	112	yellow needles	16·6	16·6
amyl	99	yellow needles	15·7	15·4
isoamyl	87	glazed yellow needles	15·7	15·6
heptyl	50	yellow needles	14·2	14·4
ethylene diamine	280	yellow solid	20·0	20·2
dipropyl	-	oil	-	-
di-isobutyl	-	oil	-	-
diamyl	-	oil	-	-
benzyl	100	yellow needles	14·6	14·4

As can be seen from the table, the secondary amines do not react to give solid derivatives. The melting points of the derivatives obtained from the

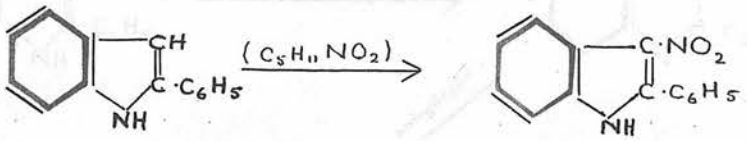
primary amines are all rather close together and the crystalline structures are almost all the same. Thus it is difficult to make a distinction between the various members of the series. The derivatives of the normal chain amines, e.g., methylamine, amylamine, etc., separate more rapidly than do those of the branched chain compounds, like isobutylamine and isoamylamine.

Frankland, etc. (J.C.S., 1919, 115, 162) have prepared the 2:4:5-trinitrotoluene derivative of methylamine and obtain a melting point of 176°C. also. Brady (J.C.S., 1921, 119, 101 and 1924, 125, 2400) has prepared derivatives with m-toluidine and studied the reactions with aromatic amines. It has never been adopted as a general reagent for amines up to the present.

IV. ALKYL NITRITES.

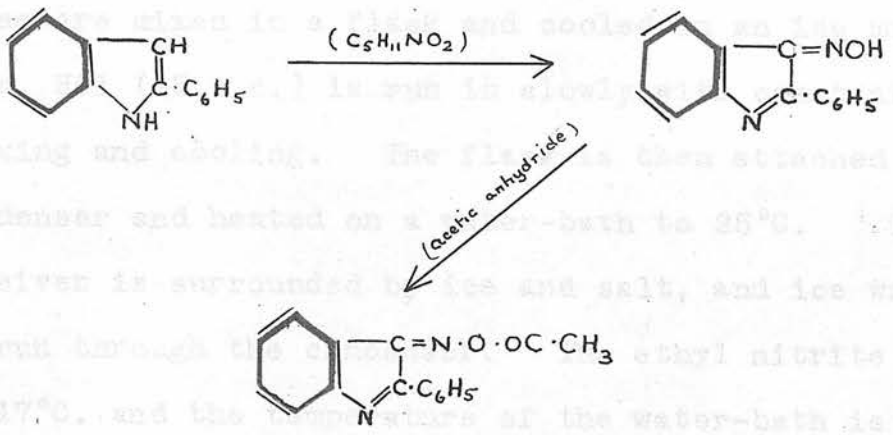
Alkyl nitrites as a class are not always easy to identify. One reaction, however, takes place very readily; that is, the reaction with α-phenylindole. Spica and Angelico (Chem. Cent. Blatt, 2, 1899, 717) found that the action of α-phenylindole on amyl nitrite produced glazed golden-yellow scales of isonitroso-α-phenylindole, m.p. = 250°C. Campbell and Cooper (J.C.S., 1935, 1208) prepared the same compound from sodium nitrite and α-phenylindole and after several crystallisations raised the melting point to 280°C. They found the best crystallising agent to be amyl acetate, the isonitroso compound being practically insoluble in boiling alcohol, glacial acetic acid and all the common organic solvents.

We tried a modification of the method of Spica and Angelico. Equal amounts, 0·5 g. approx., of amyl nitrite and α-phenylindole were heated slightly in a test-tube. A yellow solid separated on cooling, m.p. = 242-243°C. After one crystallisation the m.p. was 243°C. and a mixed melting point with β-nitro-α-phenylindole was 240-243°C. Therefore, the reaction is too violent and the nitro compound is formed.



The α-phenylindole used was prepared by the method of Fischer (Ann., 1886, 236, 116).

In the next experiment, about 0·2 g. α-phenylindole was dissolved in just sufficient alcohol for solution, and 0·2 g. amyl nitrite added. On cooling, an orange solid separated with m.p. = 268°-270°C. After two crystallisations from amyl acetate, orange-yellow diamond-shaped needles, m.p. = 280°C., were obtained, which is in agreement with the β-isonitroso-α-phenylindole obtained by Campbell and Cooper. To confirm this the acetyl derivative was prepared by boiling a portion of the isonitroso compound with excess acetic anhydride for several minutes. On cooling and adding water and solid sodium carbonate to neutralise the acetic acid formed, a red solid separated. This was filtered, thoroughly washed with water and crystallised from ligroin. Small red needles, m.p. = 115-116°C., were formed. After two more crystallisations, deep-red needles forming clusters, m.p. = 121°C., were obtained in agreement with Spica and Angelico, and proving the presence of the isonitroso compound.



Theoretically 1·9 g. α-phenylindole require 1·17 g. amyl nitrite for complete conversion. 0·1 c.c. amyl nitrite is approximately equivalent to 0·07 g. Using these figures, we found that the nitrite could be detected as isonitroso-α-phenylindole down to 0·005 g. by preparing solutions of the nitrite in alcohol. If left standing for several hours, about one milligram of nitrite can be detected.

The reaction was now applied to other aliphatic nitrites and was found to apply equally well to all the normal and branched chain nitrites tried. The nitrites were all prepared in a similar way from sodium nitrite, hydrochloric acid and the corresponding alcohol.

Ethyl Nitrite. (Gattermann and Wieland, "Laboratory Methods of Organic Chemistry", p.137)

$$C_2H_5OH + NaNO_2 \xrightarrow{(HCl)} C_2H_5NO_2 + NaOH$$

37 g. sodium nitrite

70 c.c. water

60 c.c. ethyl alcohol

These are mixed in a flask and cooled in an ice mixture; conc. HCl (42 c.c.) is run in slowly with constant shaking and cooling. The flask is then attached to a condenser and heated on a water-bath to 25°C. The receiver is surrounded by ice and salt, and ice water is run through the condenser. The ethyl nitrite distils at 17°C. and the temperature of the water-bath is never allowed to rise above 40°C. The nitrite is dried over solid potassium carbonate for a short time and is then pure enough for our purpose.

Yield = 25 g. (62% theory).

The derivative with α-phenylindole separates after a minute in the characteristic form of the isonitroso compound, and after two crystallisations the melting point is 279°C.

n-Propyl Nitrite $C_3H_7NO_2$.

The preparation is the same as that for ethyl nitrite except that n-propyl alcohol is used and the solution heated on the water-bath to 50-60°C. instead of 25°C.

b.p. of nitrite = 46°C.

Yield = 25 g. (53% theory)

The derivative with α-phenylindole separates immediately, and after two crystallisations from amyl acetate the melting point is 279°C.

Isopropyl Nitrite. $CH_3 \diagdown \diagup CH.NO_2$ CH_3

The preparation is similar to above.

b.p. = 39-42°C.

Yield = 30 g. (64% theory)

The derivative with α-phenylindole after one crystallisation has a melting point of 280°C.

n-Butyl Nitrite. $C_4H_9.NO_2$

In this case the water-bath is heated to 80-90°C. The butyl nitrite formed has b.p. = 65-70°C.

Yield = 36 g. (65% theory)

The derivative with α-phenylindole separates at once with a melting point of 280°C.

The reaction has been tried with sodium nitrite and ethyl nitrate but was negative in both cases. Therefore the reaction is specific for organic nitrites and can be used for the classification of aliphatic nitrites. With α-methylindole and amyl nitrite, only an oil was formed, thus showing α-phenylindole to be the better reagent. Unfortunately the preparation of the reagent is rather costly, but since the reaction is so sensitive very little is required for each experiment. The reaction can be applied in the reverse manner as a test for α-phenylindole.

Owing to the large and rapid precipitation

of the isonitroso-α-phenylindole we applied the reaction quantitatively in the hope that it might be useful as a quantitative estimation of nitrites. At present the methods used require special care, and if this were applicable it would be a very simple method. The outline of the method is to take a known solution of a nitrite and add to it sufficient α-phenylindole for complete conversion. After a suitable period the precipitate is filtered through a tared Gooch crucible, washed with alcohol and dried at 100°C. After obtaining a constant weight, the weight of precipitate can then be calculated. Consequently a solution of butyl nitrite in alcohol was prepared.

100 c.c. solution contain 1·0735 g. butyl nitrite

∴ 10 c.c. " " 0·10735 g. " "

Again theoretically:

103 g. butyl nitrite require 193 g. α-phenylindole to form 222 g. isonitroso-α-phenylindole.

∴ 0·10735 g. butyl nitrite require 0·201 g. α-phenylindole to form 0·2316 g. isonitroso-α-phenylindole.

10 c.c. of the above standard solution are used for each determination.

Experiment 1.

0·21 g. α-phenylindole were dissolved in sufficient alcohol, and 10 c.c. nitrite solution added. This was heated gently and left for 1 hour, then filtered, dried and weighed in a tared Gooch crucible.

Weight of precipitate = 0·0667 g.

On repetition: " " " = 0·0693 g.

Theoretically the weight of precipitate should be 0·2316 g. (see above). Therefore, the reaction is not nearing completion or else a side reaction is taking place, the product of which is soluble in alcohol.

Experiment 2.

This was left standing for 24 hours.

Weight of precipitate = 0·0779 g.

The reaction may be too violent and possibly could be remedied by allowing it to take place in the cold: that is, by dissolving the indole in alcohol without heating, then adding the nitrite and leaving. A qualitative experiment carried out beside the quantitative in Experiment 2 showed us that the β-nitro-α-phenylindole was formed. This is soluble in alcohol and would therefore account for the loss in weight. Control experiments showed that the β-isonitroso-α-phenylindole is extremely insoluble in alcohol. Thus, heating must favour the formation of the nitro compound.

Experiment 3.

This was carried out in the cold and left for 1 hour.

Weight of precipitate = 0·0751 g.

A control qualitative experiment showed that the isonitroso compound was formed but that the reaction was not going to completion. A catalyst was possibly required to hasten the hydrolysis. Dilute hydrochloric acid was used.

Experiment 4.

4 drops dil. HCl were added and reaction left for 1 hour.

Weight of precipitate = 0·1611 g.

Error = 30%

The time for precipitation was probably not long enough.

Experiment 5.

2 drops of dil. HCl were added to the cold solution which was allowed to stand for 2 hours.

Weight of precipitate = 0·1702 g.

This was washed with alcohol and dried at 100°C.

Weight of precipitate = 0·1699 g.

The loss in weight was negligible, as it ought to be, because of the insolubility of the isonitroso compound.

Error = 25%

Experiment 6.

This was left for 18 hours with 2 drops dil. HCl

Weight of precipitate = 0·1682 g.

Thus, the hydrolysis was not completed by leaving for a time or by the addition of a catalyst.

A blank experiment was now done to determine whether another reaction had occurred. A known quantity of β-isonitroso-α-phenylindole was placed in a tared Gooch crucible, treated with amyl nitrite and alcohol, dried and weighed.

Weight before treatment = 0·1594 g.

" after " = 0·1522 g.

∴ Loss in weight = 0·0072 g. 4·5%

Treated again with amyl nitrite:

Weight of ppt. = 0·1434 g.

∴ Loss in weight = 0·0088 g. 5%

The amyl nitrite appeared to have some effect. An experiment similar to No. 5 was done with amyl nitrite instead of butyl nitrite, with the same results.

Weight of amyl nitrite taken = 0·1734 g.

0·1734 g. amyl nitrite theoretically yields 0·329 g. isonitroso compound

" " " practically yields 0·2085 g. isonitroso compound

after standing in the cold for 2 hours.

This gives an error of 36%. A control experiment was now done to find if the nitrite used was 100% pure. The method used was that of Dott (Pharm. J. 1914, 4, 38, 164). Special care has to be taken to exclude all air from the reaction or high results are obtained. By this method the butyl nitrite was found

to be 97% pure, and the amyl nitrite 96% pure. Therefore, the error in our method could not be accounted for by the impurity of the nitrites.

Evidently something fundamental is wrong, and until this is discovered, the method cannot be adopted for a quantitative method of estimating aliphatic nitrites. The 25% error must be due to some side reaction taking place, the product of which is soluble in alcohol. Sufficient α-phenylindole was used for the complete precipitation of the isonitroso compound. In one experiment, excess α-phenylindole was used. Again a similar error was obtained. If the reaction were reversible it would account for the error, but because of the insolubility of the product in alcohol this possibility has to be excluded.

V. MONOBASIC ACIDS.

Monobasic aliphatic acids react with o-phenylene diamine in the presence of dilute hydrochloric acid to form 2-substituted benziminazoles according to Phillips (J.C.S., 1928, 2393). The dibasic acids, e.g., oxalic, malonic and succinic acids, do not yield the benziminazoles but various other compounds or mixtures of compounds are obtained. Thus malonic acid gives rise to o-phenylenemalonamide and 2-aminomalonanilic acid. Aromatic monobasic acids, like benzoic acid, only give a trace of benziminazole which can only be isolated as the picrate. We therefore confined our attention to the monobasic aliphatic acids with one or two exceptions, which were used chiefly for the sake of comparison.

Those monobasic aliphatic acids soluble in water are not very easy to identify, or to obtain in the anhydrous state from solution. Most of the methods used for identification are not available for aqueous solutions, and it would be a great advance to be able to detect and identify the acids in dilute solution. Since doing this work American workers, Pool, Harwood and Ralston (J.A.C.S., 1937, 59, 178) have published a paper on the use of 2-alkylbenziminazoles

in the identification of monobasic acids. However, the benziminazoles formed by Phillips do not differ greatly in melting points and are therefore not much use for identification purposes. These are obtained by refluxing 0·02 mol o-phenylene diamine with 0·03 mol acid and 20 c.c. 4 N. HCl for 30-40 minutes. Ammonia is then added, when the benziminazole separates and is crystallised from water or aqueous alcohol. Those obtained by Phillips and their melting points are quoted below.

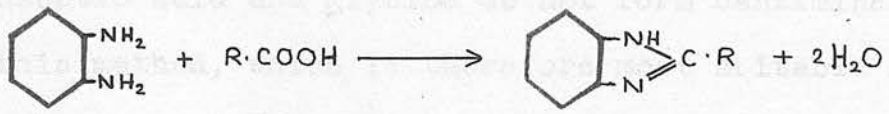
Acid.	m.p. of benziminazole.
Formic	170
Acetic	176
Propionic	177
Glycollic	171-172
Mandelic	202-203
Lactic	178-179

Benziminazole itself readily forms a picrate which has been prepared and is quoted in the literature. The 2-substituted compounds should, therefore, form picrates readily and thus prove a good means of identification. 0·5 g. o-phenylene diamine, 0·5 - 1·0 g. acid and 3-4 c.c. of 4 N. HCl are refluxed for 15 minutes. On cooling, conc. ammonia is added until the solid benziminazole separates. This is filtered off, washed well with water and dissolved in the minimum

amount of alcohol. A saturated alcoholic solution of picric acid is then added, and the whole allowed to cool, when the picrate separates. This is crystallised from alcohol until the melting point is sharp, and the picrate therefore pure. This procedure has been used for all the acids mentioned in the table. In several cases when the picrate was sparingly soluble in alcohol, the other common organic solvents and glacial acetic acid were tried. In such cases, a large volume of alcohol has been found to be the most suitable.

In the cases of formic and acetic acids it is possible to obtain the benziminazole by heating with o-phenylenediamine and HCl in a test-tube for 1-2 minutes. On cooling and adding ammonia, the benziminazole separates. Again with very dilute aqueous solutions of these acids the benziminazole is obtained. For the lower members of the series the reaction is very sensitive and the acid can be detected in dilute solutions. This is true for all the acids soluble in water. The fatty acids from formic to undecylenic have been tried, and those up to n-caproic $C_5H_{11}.COOH$ yielded the benziminazole picrate readily, with the exception of isovaleric acid, which did not react at all. Caprylic, pelargonic and undecylenic acids were unreactive also, but since they are not so soluble in water, they are easily detected by other methods. The only aromatic acid yielding the picrate is mandelic acid.

The reaction is simply a linking together of the two molecules with the elimination of two molecules of water resulting in a ring compound.



The picrate is, as usual, a molecular compound of picric acid with the 2-substituted benziminazole. The picrate of o-phenylene diamine has also been prepared in order that any picrates with a similar melting point could be distinguished by means of a mixed melting point with o-phenylene diamine picrate. This latter separates from alcohol in deep-yellow needles which decompose at 208°C. This distinguishes it from the benziminazole picrates, none of which decompose.

Analysis: %N Calculated = 25·9%

Found = 25·4%.

The halogen acids were tried but proved to be rather disappointing. The picrates formed are very sparingly soluble in alcohol and most other solvents, and so are difficult to crystallise. Iodoacetic acid yields a very dirty, oily solid as the benziminazole which is not converted into the picrate. However, β-iodopropionic acid yields a white solid benziminazole which forms a picrate with a lovely crystalline structure, easy to crystallise. This must be due to the iodine atom being removed from the

carboxy group. Chloracetic, dichloracetic and bromacetic acids yield picrates which are difficult to purify and do not have a good crystalline structure. Cyanacetic acid and glycine do not form benziminazoles by this method, which is therefore most suitable for the unsubstituted aliphatic monobasic acids. Lactic, mandelic and glycollic acids all react very readily, forming beautiful picrates, but pyruvic acid is unreactive. This is probably due to the ketonic grouping present.

Several experiments have been performed to show the advantages of this method. Methyl formate was refluxed for about 10 minutes with 4 N. HCl, then o-phenylene diamine added. After another 5 minutes this was cooled and ammonia added, when the benziminazole separated. This was transformed into the picrate, of which there was a good yield. Thus the acid in dilute solution can readily be detected and identified. Hydrolyses of ethyl acetate and methyl acetate required a longer time but yielded the picrate in the same manner.

The results and analysis figures are tabulated below. As before, dashes indicate that results were negative and blank spaces that the compound has already been prepared.

2-Alkylbenziminazole Picrates.

Acid.	2-Substituted benziminazole	Picrate.			
		Crystalline Appearance	M.p. in °C.	%N.Calc.	%N. found
Formic	H	orange needles	230		
acetic	methyl	needles	214	19·4	19·6
propionic	ethyl	plates	120	18·7	18·6
butyric	propyl	plates	124	18·0	18·1
isobutyric	isopropyl	plates	136	18·0	17·8
isovaleric	-	-	-	-	-
caproic	amyl	plates	282	16·8	16·6
caprylic	-	-	-	-	-
pelargonic	-	-	-	-	-
undecylenic	-	-	-	-	-
lactic	α-hydroxy ethyl	plates	131	17·9	17·8
pyruvic	-	-	-	-	-
glycollic	hydroxy methyl	needles	214	18·6	18·5
mandelic	α-hydroxy benzyl	needles	209	15·5	15·2
monochloracetic	chloromethyl	solid	186	17·7	17·9
dichloracetic	dichloromethyl	solid	270	14·8	15·1
trichloracetic	-	-	-	-	-
monobromacetic	bromomethyl	oil	-	-	-
iodoacetic	-	-	-	-	-
cyanacetic	-	-	-	-	-
β-iodopropionic	β-iodoethyl	plates	140	14·0	14·0
crotonic	-	-	-	-	-
glycine	-	-	-	-	-

VI. PREPARATION OF 2:4-DINITROBENZOIC ACID.

A suitable method for the preparation of 2:4-dinitrobenzoic acid from phenylacetic acid has been discovered as the chance result of a test-tube experiment. The yield and purity are very good. We thought that it might prove a less expensive reagent for the identification of alcohols, by the formation of esters, than the 3:5-dinitrobenzoic acid generally used. This latter is rather difficult to prepare. Not with nitric.
A small-scale experiment was first carried out for the preparation of the 2:4-dinitrobenzoic acid which is described below.

10 g. phenylacetic acid
100 c.c. fuming nitric acid

These were gently boiled under reflux for 45 minutes and then poured into water. On cooling, a yellow crystalline solid separated, which was filtered, thoroughly washed with water and dried. On standing, a second crop of crystals was obtained from the filtrate. The yield of the crude material was 12·5 g. (91·3% theory). This was divided into two portions.

1) 6·5 g. were dissolved in about 200 c.c. boiling water and on cooling, pale-yellow needles were obtained.

m.p. = 181-183°C.

quoted m.p. = 182-183°C.

yield = 5·5 g. (85%)

2) 6 g. were crystallised from 15 c.c. (approx.) of glacial acetic acid. Pale-yellow needles were again obtained, but a great amount was lost by crystallisation.

m.p. = 179-183°C.

yield = 3 g. (50%)

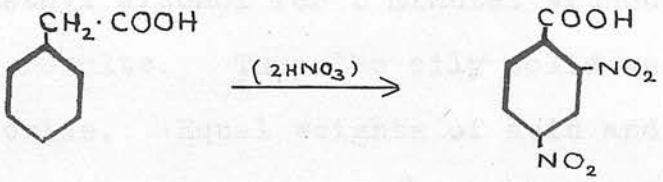
Thus, the better crystallising agent is water, the resulting compound being purer and the yield larger than that from glacial acetic acid.

The preparation was then tried on a larger scale, using 50 g. phenylacetic acid and 500 c.c. fuming nitric acid. Care had to be taken in adding the nitric acid to the phenylacetic acid, to add it slowly, with cooling. The solution was refluxed for one hour and then poured into water. The solid was filtered, thoroughly washed with water until the filtrate showed no acid reaction, and dried.

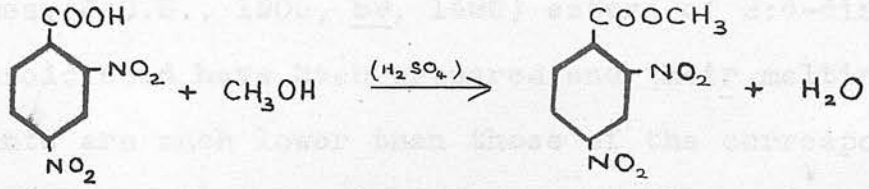
yield = 51 g. (70%)

m.p. = 180° - 183°C.

The product is crystalline and, due to the thorough washing, quite pure enough for all practical purposes, so that crystallisation is quite unnecessary.



An attempt was made to identify this acid by the preparation of the α-naphthylamine - 2:4-dinitrobenzoate by means of α-naphthylamine (Beuhler, Culfree, J. Ind. Eng. Chem. (Anal.) 1934, 6, 351). This was, however, unsatisfactory, so the methyl ester was prepared by refluxing 0·5 g. 2:4-dinitrobenzoic acid with 5 c.c. methyl alcohol and 0·5 c.c. conc. H_2SO_4 for 1½ hours. On cooling and diluting with water, the ester separated as a white solid, m.p. = 50-55°C. On crystallising from hot water, white needles separated, m.p. = 67-68°C. (quoted m.p. = 70°C.). The acid is, therefore, 2:4-dinitrobenzoic acid.



Attempts were now made to prepare the acid chloride of 2:4-dinitrobenzoic acid in order to prepare esters easily from alcohols. 0·5 g. acid was mixed with 1 g. phosphorous pentachloride, and gently heated to start the reaction, then boiled for 4 minutes. This was cooled and pressed on a porous plate, when a very oily solid was obtained. This was refluxed with

1 c.c. methyl alcohol for 5 minutes without any positive results. Thus the oily solid was not the acid chloride. Equal weights of acid and thionyl chloride, $SOCl_2$, were now refluxed for 1 hour. Excess thionyl chloride was removed by suction in vacuo, when a dark, oily solid was formed. This was crystallised from petrol ether, 40/60, when white crystals, m.p. = 65-67°C., were obtained. This was a mixture of acid and acid chloride. Several more attempts at each method, varying the conditions, were unsuccessful, and this is due to the fact that the melting point of the acid chloride is 40°C. The preparation of these esters by the Fischer-Speier method is very lengthy compared to the time required for the esters of the 3:5-dinitrobenzoic acid. The methyl, ethyl (Curtius, Bollenbach, J. prakt. Chem., 1907, 76, 287) and menthyl (Cohen, Aimes, J.C.S., 1906, 89, 1480) esters of 2:4-dinitrobenzoic acid have been prepared and their melting points are much lower than those of the corresponding esters of 3:5-dinitrobenzoic acid. Thus, the 2:4-acid is of little use as a reagent for alcohols, although the method of preparation is new and a great improvement on those already known, such as that of Curtius and Bollenbach. They prepare the acid from 2:4-dinitrotoluene by oxidation with conc. H_2SO_4 and chromic acid. The method requires careful adjustment of the temperature

and a long time compared to that of our method which is very simple and requires little attention.

D I S C U S S I O N.

The aim of this research has been to find suitable qualitative tests for the identification of certain classes of organic compounds by the preparation of crystalline derivatives, using not more than 0·5 g. of the compound to be identified. In some cases several reagents have been tried in order that the most suitable might be selected. An improvement on previous reagents has been made in the majority of compounds tried. Our main object has been to prepare derivatives from as little as possible of the compound and to use reagents which are applicable to a whole class of compounds and not to one or two isolated members.

Oxidation of Side-chains.

The sealed tube method has proved to be very satisfactory and was successful in forty out of forty-eight experiments. The time of the experiment has been considerably shortened from that of the permanganate or dichromate methods, and the purification is, in many cases, much simpler. It is rather remarkable that in none of these cases did any nitration occur. Those compounds which did not oxidise readily with nitric acid

in sealed tubes were mostly rather highly substituted. Some were very explosive, causing the tube to disintegrate during the heating or to open violently, so that any solid formed was lost. For example, mesitylene and o-nitrotoluene reacted very violently, and in the former case no product was obtained. In the latter case there was sufficient material formed for identification. This has been overcome by using hard glass tubes for the oxidation. It is not, however, practicable for the use of students in the laboratory as an oxygen blowpipe flame is required to seal the tube, whereas the soft glass tubes can readily be sealed in an ordinary blowpipe flame. Although in some cases the yields were not very large, sufficient was always obtained for the identification of the acid. The method is useful in the distinction of the xylenes, all of which have similar boiling points. By their oxidation to the toluic acids they can readily be identified. Toluene, ethylbenzene, iodotoluenes and many others are very difficult to oxidise with potassium permanganate. In fact, it is almost impossible, but by varying the time and temperature in the sealed tube method, the yields of acid obtained can be extremely good. In cases of easy oxidation, of course, permanganate has its advantages

Alkyl Halides.

The formation of isothiourea picrates is applicable to all alkyl iodides and bromides, and the identification of each member is assured. The method is simple and can be completed in a very short time. This again stresses the advantage over the procedures involving the use of the Grignard reagents. The crystalline structures of the resulting picrates are very distinct, and assist greatly in the identification of the alkyl group. The reaction is very sensitive, ethyl iodide having been detected to 0·005 g. in alcoholic solution. This yields sufficient picrate for a melting point and an examination of the crystalline structure which can be compared with the photographs shown in this thesis. The method seems to be much superior to any previously used. It is unfortunate that the chlorides do not react as readily with thiourea.

Aliphatic Amines.

The best reagent of those isothiocyanates tried for aliphatic amines is β-naphthylisothiocyanate. Many of the reagents already used are very good for the free amines but are useless for amines in aqueous or alcoholic solutions. The phenylisothiocyanates have the advantage that they react with the amine readily

in 10% solutions of water or alcohol, yielding sufficient derivative for identification. The use of 2:4:5-trinitrotoluene as a reagent for amines is not general for aliphatic amines, since it only reacts with the primary amines. The reaction is, nevertheless, extremely delicate and enables a trace of amine to be precipitated immediately as a 2:4-dinitro-5-aminotoluene. In this it has an advantage over the isothiocyanates, but as a general reagent for aliphatic amines β-naphthyl-isothiocyanate is much to be preferred. The amine derivatives of the trinitrotoluene cannot be identified by their crystalline structure, since they are similar in nearly every case. The melting points, likewise, are not dependable because many are rather close together: for example, 2:4-dinitro-5-amylaminetoluene melts at 99°C. and the butylamine at 96°C. The same may be noticed with the propylamine, butylamine and amylamine derivatives of β-naphthylisothiocyanate whose melting points are respectively 114°C., 119°C. and 114°C. but whose crystalline structures are distinct, being plates, needles and prisms respectively. Thus, on the whole, β-naphthylisothiocyanate is the better general reagent for aliphatic amines, and 2:4:5-trinitro-toluene is useful for the detection of traces of primary aliphatic amines.

Alkyl Nitrites.

Little remains to be said under this heading except that a reagent for the classification of alkyl nitrites has been discovered in α-phenylindole. It is unfortunate that the source of error in the quantitative estimation of nitrites could not be ascertained, as undoubtedly it would prove a very simple method for the determination of alkyl nitrites.

Monobasic Acids.

The formation of 2-substituted benziminazole picrates has proved to be very satisfactory in the identification of monobasic aliphatic acids. The method is most suitable for the unsubstituted acids but can be used for certain halogen substituted acids, especially if the halogen group is in the β-position to or further away from the carboxylic group. In the α-position the reaction does not take place nearly so readily. The melting points of the picrates are reasonably far apart and so are suitable for identification purposes. The melting points of the benziminazoles themselves are too close together for distinction, as is shown in Phillips' results (loc. cit.). The method is very useful for those acids soluble in water. Thus, if an ester requires identification it can be hydrolysed with hydrochloric acid for the requisite time. o-Phenylene diamine can then be added and

after 15 minutes refluxing, the benziminazole picrate can be prepared and isolated in the manner already shown. A very small quantity of acid in a comparatively large volume of water can thus be isolated as the 2-substituted benziminazole picrate, in a sufficient quantity to determine the melting point of the purified compound. The only other method which does not require the anhydrous acid is that of the p-bromophenacyl esters and, as already mentioned, the melting points of these derivatives are not always very good.

Reagents which adhere to the rules given on page 2 have been used satisfactorily for aliphatic amines, alkyl halides and monobasic acids. A reagent for the classification of alkyl nitrites has been obtained, and a method of identifying substituted aromatic hydrocarbons by oxidation to the corresponding acids has been worked out. All the derivatives formed are stable compounds, very few of which even decompose on heating. Most have sharp melting points and definite crystalline structures. In every case where a new compound has been prepared an analysis has been carried out. Thus, there is no doubt as to the nature of the compound prepared.

S U M M A R Y.

The object of this work has been to find suitable qualitative tests for some classes of organic compounds. The reaction must be applicable to 0·5 g., or less, of the compound, and to every member of the series. The resulting derivative must have a good crystalline structure and melting point; must be easily prepared and be stable. .The melting points of such derivatives must differ by at least 5°C. from one member to the next.

Substituted hydrocarbons have been oxidised in sealed tubes with nitric acid (sp. gr. 1·2) to the corresponding acids. 0·5 g. substance and 5 c.c. acid were used in each experiment. The yields and melting points of the acids obtained and the peculiarities of each experiment have been noted.

Alkyl bromides and iodides have been converted into S-alkylisothiourea picrates by the use of thiourea. The picrates are stable, have good melting points, and remarkable crystalline structures. Photomicrographs of these latter have been prepared and can be used in the identification of the compounds.

Aliphatic amines have been identified by the use of various substituted phenylisothiocyanates.

β-naphthylisothiocyanate has been found to be the most suitable. The amine derivatives have good melting points, crystalline structures, and separate readily from solution. 2:4:5-Trinitrotoluene has been used to detect primary aliphatic amines in small quantity but is useless as a general reagent for aliphatic amines.

α-phenylindole has been used for the classification of alkyl nitrites, β-isonitroso-α-phenylindole being formed. The use of this reaction as a qualitative estimation of nitrites has been abandoned, due to a 25% error which could not be detected.

Aliphatic monobasic acids have been identified by the formation of 2-substituted benziminazole picrates. The reaction is not quite general, but is exceedingly useful for those acids soluble in water.

2:4-Dinitrobenzoic acid has been prepared from phenylacetic acid and fuming nitric acid. The yield is almost quantitative and the purity good, but as a reagent for alcohols it is inferior to the 3:5-dinitrobenzoic acid already in use.

In conclusion, the author would like to thank Dr Neil Campbell for his valuable advice and supervision during the course of this research. This was carried out during the tenure of the Mackay Smith Scholarship for which grateful acknowledgment is made

to the University of Edinburgh.